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DATABASE ANALYSIS OF ETHNICITY, SEX, AND INSURANCE STATUS OF PATIENTS WITH PARKINSON'S DISEASE

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ABSTRACT

Parkinson's Disease (PD) is the second most common neurodegenerative condition in humans, after Alzheimer's disease. It can be observed in all races and both genders, in the United States and worldwide. However, disparities in disease progression and manifestation exist between races and sexes. In addition, treatment options and overall health, impacted by insurance type, may affect a PD patient's disease state. The purpose of this study is to contribute to the background demographic information of PD patients, particularly as pertaining to insurance classification, which has not yet been addressed in the literature.

The Hoehn and Yahr (H&Y) scores of patients both ON and OFF medication, a method of ranking and analyzing disease severity in Parkinson's patients, were analyzed in this study. The hypothesis is that the H&Y scores are impacted by race, gender, and insurance status. A univariate analysis of each variable was performed, the Student's t-test was used for gender and insurance status and a One-way ANOVA for race. A multivariate regression model analysis was then run for the primary outcomes and included all the variables and known confounders. A secondary analysis of disease complications utilizing Chi-square tests and logistic regression was also performed.

Gender and insurance status did not differ significantly in H&Y scores. Black or African patients had a significantly increased PD progression as compared to Caucasian patients. Males and females differed significantly with regard to several disease complications. Subjects with public insurance also exhibited greater odds of some disease complications as compared to subjects with private insurance.

In agreement with the literature, black PD patients exhibited a greater disease progression as compared to white PD patients. However, the reason for this has not yet been adequately addressed. In addition, more studies are needed to analyze other racial groups that were too small to appropriately address in this study. Despite a lack of difference in H&Y scores, PD is observed to be manifested differently between genders (disease complications), also in agreement with the literature. More studies are required to discover the reason for this disparity. Insurance classification does not impact H&Y scores. However, more studies are required to address whether this is maintained with a more sensitive outcome measure, such as the UPDRS. In addition, some complications differ between insurance categories, implying a disparity in treatment options and therapies.

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LIST OF ABBREVIATIONS

COMT ..... Catechol-O-Methyltransferase

DBS ..... Deep Brain Stimulation

DDIs ..... Decarboxylase Inhibitors

GPi ..... Globus Pallidus Internus

H&Y ..... Hoehn and Yahr

IRB ..... Institutional Review Board

L-dopa ..... Levodopa

LBs ..... Lewy Bodies

MAO ..... Monoamine Oxidase

MPTP 1-Methyl-4-Phenyl, 1, 2, 3, 6-Tetrahydropyridine

NIH ..... National Institutes of Health

PD ..... Parkinson's Disease

SN ..... *Substantia Nigra*

STN ..... Subthalamic Nucleus

TCE ..... Tricholoroethylene

UPDRS ..... Unified Parkinson's Disease Rating Scale

INTRODUCTION

Parkinson's Disease (PD) was first described by James Parkinson in his 1817 paper titled *An Essay on the Shaking Palsy.*[1] However, this article did not garner much attention at the time, and was overlooked until the 1860s, when Jean-Marie Charcot used it to distinguish a condition he termed Parkinson's Disease. Charcot thoroughly explored this condition during his career, and he recorded many of the symptoms that are still used to characterize PD today.[2]

PD is the second most common neurodegenerative condition in humans, after Alzheimer's disease. The mean age of onset of the disease is in the early 60s, but up to 10% of those with the condition have an onset prior to age 40.[3]

Total annual health-care costs are almost $12,000 greater for PD patients in the United States as compared to non-PD controls, and these values only increase as the disease progresses.[4] The annual cost of PD in the United States is nearly $23 billion. With a projected population of 80 million Americans who will be over 65 years of age in 2040, a conservative estimate of PD cost at that time will be $50 billion annually.[3]

Signs and Symptoms

The external appearance of the brain in PD is often unremarkable, with no significant atrophy in the brainstem, white matter, or cortical brain areas. Sections of the brainstem usually reveal a loss of dark pigmentation in an area named the *substantia nigra* (SN),

which translates to “black substance”. This loss of coloration in the SN correlates with neuronal loss.[5] Neurons found in the SN area contain dopamine, a neurotransmitter important in relaying messages within the motor centers of the brain.[6] Accompanying this deficiency of neurons is the added accumulation of protein aggregates named Lewy Bodies (LBs). LBs are composed of filamentous material that includes the protein α-synuclein exhibiting an abnormal conformation, and they are considered a hallmark of PD. In addition to the LBs, tiny projections, also made up of α-synuclein, are observed growing from neurons and are referred to as Lewy neurites.[1]

The progression of PD has been characterized by the Braak staging system, which has been derived from autopsy studies of normal brains and those associated with LB-related diseases.[5] Stage 1 of the Braak stages is observed when Lewy neurites are found in the dorsal motor nucleus and the olfactory bulb, and this pathology worsens in stage 2. Both of these stages are considered “pre-symptomatic”; although symptoms may be present, they are usually overlooked. In particular, the damage to the olfactory bulb results in a loss in the sense of smell, an early warning sign of PD pathology.[7] Also, during stage 2, the progression of the disease into the lower brainstem could result in many potential sleep or gastrointestinal symptoms.[1] Therefore, if PD could be diagnosed at these early stages, the loss of neurons from the SN could be prevented, with adequate treatment. Stage 3 is when the disease progresses to the SN and the forebrain, and the first Lewy neurites are visible in these areas. Stage 4 is a continuation of this progression, with the extent reaching further into the cortex to Ammon’s horn and the temporal mesocortex. It

is somewhere during the course of these two stages that the patient moves from the "pre-symptomatic" phase into the "clinically-apparent" stage of PD, and motor symptoms manifest. In the final stages, 5 and 6, the neurodegenerative process culminates – the SN appears pale and LBs are found in the cerebral cortex. At this point, patients manifest the full range of PD-associated symptoms.[7] The Braak classification, while useful, is somewhat controversial, as it relies on Lewy neurite formation alone, and not on neuronal degeneration. In addition, the pathological progression as outlined by Braak is not seen in all PD brains.[1]

Due to the controversy of Braak's stages and their reliance on autopsy verification, other forms of assessing disease progression have been developed that instead focus on symptoms. A commonly used system is the modified Hoehn and Yahr, a classification that has been enhanced since its first emergence in the 1967 paper.[8] This system begins at stage zero, in which there are no signs of the disease up to stage five, when the patient is wheelchair-bound or bedridden. However, PD is a very complex disease with indicators that manifest in several areas other than motor symptoms. The Unified Parkinson's Disease Rating Scale (UPDRS) is a composite scale that includes several aspects of PD such as mood, cognitive symptoms, activities of daily living, disease severity, and a disability scale.[9] The UPDRS has also been modified and includes the modified Hoehn and Yahr scale as part of its analysis.[10]

Early symptoms of PD may be nonspecific – fatigue, muscle cramps, joint stiffness, sleep disturbances, constipation, and bladder dysfunction.[11] In addition, other signs may emerge, such as a stooped posture, limping or dragging of one leg, a loss of the sense of smell, and a softness of voice.[6] The loss of dopamine from the *substantia nigra* results in classical symptoms of PD, characterized by the acronym TRAP. T is for "tremor. R is for "rigidity" (muscle stiffness). A is for "akinesia" (loss 0f voluntary movement and fluid motion). P is for "postural instability" (difficulties with balance and gait).[6]

The age of onset of PD is usually between 50 and 60 years, but can actually range from childhood to eighty or ninety years of age. The progression of the disease is just as variable as the age of onset. Overall, the average amount of time in each Hoehn and Yahr stage (0-5) is estimated to be two-three years, and the average decline in the UPDRS is approximately two and a half points per year. Without medication, PD has a thirteen year duration and an average age of death of 73 years. Due to recent advances in PD medication and treatment, PD mortality has been reduced and patients live longer, although they still exhibit a higher mortality rate than age-matched controls without PD.[12] Patients with PD usually succumb to secondary problems associated with the disease, the two most common of these being falls and pneumonia.[6]

Risk Factors

Aging is the single most significant factor in the clinical presentation, course, and progression of PD.[13] In any population studied, an increase in PD frequency is associated

with increasing age.[14] This can be observed across all races and both sexes,[15] in the United States,[16 17] in other countries,[18] and overall worldwide.[19] Current US prevalence values for PD are 553/100,000 for people in the age group 65-69, but rise to 2949/100,000 for people over the age of 85.[15] In some studies, a decrease in PD prevalence is observed later in life – but whether this is a true decrease or whether it is merely a difficulty in identifying PD in the very old is still unknown at this time. Should such a decrease be real, however, it would suggest a biological "window of vulnerability" in developing the disease.[14]

Head trauma has been controversial in its relationship to PD. A case study was published in 1999 regarding a patient who seemed to develop PD six weeks after an acute head trauma. A case was then made to explain why the trauma itself was the most likely cause of PD.[20] Scientists agree that head trauma can lead to PD-like symptoms,[1] and most adhere to the notion that head injuries are associated with PD,[21] but many believe that head trauma does not directly cause PD. The head trauma would have to be severe enough to disturb the dopamine system and its connections. In addition, the PD-like symptoms seen in head trauma patients diminish in time, and do not respond to well to anti-parkinson medication.[6] Despite these facts, there is a documented relation between head trauma and PD, and a dose-dependent increased risk associated with more frequent or more severe head injuries.[14] It has been stated that this type of association could be due to recall bias, in which patients with PD more easily remember and report head trauma than controls, who may forget past injuries and underreport true values. In

addition, the case has been made that head trauma and PD have a reverse causality – in other words, the motor disturbances associated with PD lead to more head injuries.[22] However, laboratory studies have suggested that chronic head injuries could affect oxygen delivery to the brain and encourage dysfunction in vulnerable systems, such as the dopamine delivery system.[14] In addition, head injury has been associated with α-synuclein accumulation in both animal models and post-mortem studies, and may initiate or accelerate the progression of the disease in individuals with already high α-synuclein levels due to mutations.[23]

Race

Racial differences between PD patients have been addressed and documented. While PD is found in all racial and ethnic backgrounds, Caucasians have a substantially higher incidence (new diagnoses of PD) and prevalence (number of patients diagnosed with the disease at any given time) of PD than blacks or Asians in the United States, with the highest incidence and prevalence found in the Midwest and the Northeast. Previous studies performed on incidence and prevalence report smaller numbers than the nationwide study performed by Wright Willis, et al, but despite the growth in incidence and prevalence, non-Hispanic whites always have higher values than blacks.[15] Despite these consistent comparisons between incidence and prevalence in white and black communities, black patients are diagnosed with PD at half the rate of white patients, even when several other potential confounding factors are controlled – factors such as age, sex, healthcare use, and geographic location.[24] What is interesting, but as yet unexplained, are

the high incidence and prevalence values in the Latino community.[16 25] Despite the lower incidence and prevalence in their community, black PD patients exhibit greater disease severity and disability than white patients. This could be due to limited access to care, economic factors,[26] or the under-reporting of symptoms that result in a later diagnosis. This under-reporting could be the result of limited social support from the family and community, or a lack of trust in physicians that treat minority patients.[27]

Gender

Sex also plays a role in PD. It has been reported that males are 1.5 times more likely to develop PD than females,[1] although some studies have found higher prevalence rates in females.[28] It has also been claimed that the pattern of risks and protective factors differ between men and women in regards to developing PD.[29] Various studies reported women have either greater,[30] less,[31] or the same disease severity as men,[32] but it is consistently observed that women report worse overall quality of life.[30 33] Women are more likely to evaluate symptoms as they relate to how they organize, build social relationships, and think, while men evaluate symptoms as they affect their appearance and strength.[34] Men exhibit an increase in weight, daytime sleepiness, dribbling saliva, interest in sex, and problems having sex,[35] while fatigue, feelings of nervousness and sadness, constipation, restless legs, and pain were more common and severe in women.[36] Depressive symptoms are more frequently observed in females PD patients and tend to be more severe – as the disease progresses, so does the frequency of depression.[37] The first symptom seen in women is most likely tremor.[32] In addition, dyskinesias are more

prevalent in women[38] and thought to be potentially caused by higher doses of L-dopa. Since women, on average, weigh less than men, they subsequently receive a higher dose per kilogram of Levodopa, as PD patients are usually treated with standard dosages without adjustment according to body weight.[39] The age of onset of PD is later in women, and positive correlations have been identified between the age of onset and the age at parity, menopause, and the length of the fertile life span.[40] Therefore, a link between PD and estrogen has been hypothesized. Recent studies have shown estrogen to be protective[41] and estrogen replacement therapies as possible treatments for PD.[30] Overall, the lifetime risk of developing PD is 4.4% for males and 3.7% for females.[3]

Environmental Conditions

Approximately 10% cases of PD are thought to stem solely from inherited genetic factors. The remaining cases are considered to be caused by some unknown environmental factors to some degree.[42]

In the 1980s, an interest was fostered in the relationship between pesticides and PD. This was brought about by the discovery that 1-methyl-4-phenyl, 1, 2, 3, 6-tetrahydropyridine (MPTP), a substance structurally similar to the herbicide paraquat, resulted in chronic PD symptoms and degeneration of dopamine-secreting neurons in humans. Since then, paraquat and many other pesticides such as rotenone, maneb, dieldrin, heptachlor, and atrazine have been extensively studied to determine if a causal link to PD could be discovered.[43] It has been stated that exposures to pesticides, herbicides, and insecticides

all increase the risk of developing PD,[44] and that this risk is dependent on the amount of exposure.[45] However, there is still debate whether pesticides, herbicides, insecticides, and fungicides increase the risk or somehow cause PD, and studies performed on specific compounds provide variable results.[43]

Paraquat is a broad-spectrum herbicide used widely in developing countries, and is one of the most commonly used herbicides worldwide, although it is restricted in the United States. Paraquat injections into mice elicit a dose-dependent decrease in movement and the number dopamine cells in the *substantia nigra.*[42] However, the link between experiments in rodents and potential human adverse effects is weak. Despite increased risks reported in many papers throughout the years,[43] some claim that the clinical evidence is inconsistent and inconclusive. Thus, more studies must be performed to answer the question of paraquat toxicity in humans, and its potential role in causing PD.[46]

Rotenone is a naturally occurring compound that is found in the roots and leaves of several plant species. It has been used extensively as an insecticide and also as a piscicide.[42] Rotenone acts through mitochondrial inhibition and is thought to interfere with normal mitochondrial pathways, thus causing dysfunction and cell death.[47] Much like paraquat, studies performed on rotenone result in variable outcomes, and it is unknown whether rotenone is a causative risk factor for PD.[43]

The risk of PD appears to be increased in rural dwellers, especially in the United States. This may be due in part to pesticide use (as described above), combined with well-water drinking, both of which occur very frequently in rural communities.[14] Drinking well water has been correlated to an increased risk of developing PD,[48] since it is thought that pesticides seep into well water through the soil, thus introducing higher amounts of chemicals with PD-associated risk to rural communities. Some studies have reported that PD patients were more likely to drink from private wells and to have drunk well water longer than controls. While rural living appears to possess a higher risk of PD attached, there is very little evidence to support a relationship between specifically rural living (and not the risk factors associated with it, such as pesticides) and PD.[43] Therefore the association is thought to be due to the combined action of pesticides and drinking well water.[49]

Rural communities are not the only population found to be at an elevated risk of developing PD. Solvents are a broad range of chemicals that act as a means to dissolve one substance into another. The most common solvents in use today are trichloroethylene (TCE), toluene, acetone, hexane, carbon disulfide – all of which serve multiple purposes. Exposure to these chemicals is usually through inhalation or through the skin.[50] Occupational exposures are common in dry cleaning, metal de-greasing, and paint stripping occupations. Although long considered as possible PD risk factors, solvents have received less attention than pesticides or metals, despite widespread use in many workplaces.[51]

TCE is a highly volatile organic chemical that has been used for many years, and is a major environmental contaminant in industrialized countries. Reports have linked PD with long-term exposure to TCE in humans, although this does not denote a causal relationship.[42] Three studies have shown that rodents given high doses of TCE orally exhibit a depletion of dopamine-supplying neurons in the *substantia nigra.* However, this does not translate well to humans, as the primary mode of exposure in humans is through inhalation, and usually at low doses. In addition, it is not known whether TCE or one of its metabolites is damaging the neurons in rodents, and if a similar model occurs in humans. At present, there is no clear toxicological or epidemiological evidence of any specific solvent or class of solvents as a cause of PD, but further research is necessary in this field.[51]

Metals are utilized in a plethora of biological processes in nearly every organism on Earth, due to properties that increase the rates of enzyme reactions, among other qualities. While toxic effects of metal exposure on the human body have been well documented, it has only been recently that the effects of metal toxicity in the brain have been addressed. Metals have long been thought to play a role in PD. Of particular interest are iron, manganese, lead, copper, and mercury.[50] Iron accumulates in the *substantia nigra* of PD patients, but this does not have a correlation with dietary iron intake, and therefore the accumulation is most likely due to environmental factors or disorders or iron uptake or transport.[42] Both copper and lead exposures have been associated with increased risk of

PD, although copper is necessary for normal human biologic functions, while lead is a non-essential metal that most often interferes with normal biologic functions.[50] In addition, combined exposures of lead-copper, lead-iron, and iron-copper all result in significant association with PD.[14] While it has been established that mercury exposure causes significant motor symptoms, and has been known to result in neurological alterations since the 1800s, there has been no established association between mercury and PD, although a major amount of data suggests that mercury exposure can impact the dopamine system in the brain.[50] Manganese is the 12th most abundant element in the earth's crust and is essential for human biology.[42] Elevated manganese exposure can occur in miners and welders, although a recent meta-analysis found a decreased risk of developing PD in the welding occupation, and no association between manganese exposure and PD.[52] While manganese exposure leads to PD-like symptoms (called manganism), and accumulated manganese in the mitochondria can cause dysfunction (a feature thought to contribute to PD), there is weak evidence linking manganese exposure to PD, and many believe manganism to be a separate entity with similar output symptoms to PD.[50]

There is also an additional risk factor to a very specific group of people. During the Vietnam War, several toxic herbicides (called Agent Orange) were used for military purposes starting in 1961, and many war veterans were exposed to Agent Orange during that time.[53] It has been reported that people (both veterans and civilians) exposed to Agent Orange exhibited an increased risk of developing PD.[54]

Identifying a single causative environmental agent that is responsible for a significant number of cases has been difficult, and as yet, still incomplete. The general conclusion is simply that it is more likely that multiple exposures over time from numerous high risk agents in conjunction with a background of genetic risk factors are responsible for most cases of PD.[42] There may be an additional effect from various exposures – one paper found that exposure to paraquat and head trauma increased the risk of developing PD more than either risk factor alone.[21]

Genetics

Up until the 1990s, PD was believed to be an environmentally caused disorder with little or no genetics component, and this is probably due to the fact that more than 70% of PD patients report no prior family history of PD.[55] However, it has been reported that a first-degree relative of a PD patient is approximately twice as likely to develop PD compared to controls,[49] although this relative risk may vary between early and late-onset PD,[56 57] between parent-to-patient relationships and sibling-to-patient relationships,[58] and between races.[59]

The genes associated directly with PD are LRRK2, PARK2, PARK7, PINK1, and SNCA. Genes that do not appear to cause PD but instead modify the risk for developing the condition are GBA and UCH-L1.[60] SNCA (also called PARK1/PARK4), LRRK2 (also called PARK8) and UCH-L1 (also called PARK5) are all considered autosomal dominant

genes, while PARK2, DJ-1 (also called PARK7), and PINK1 (also called PARK6) are all considered autosomal recessive genes.[61]

The SNCA gene codes for the protein α-synuclein, a protein whose function is largely unknown, although it has been hypothesized that α-synuclein may be involved with dopamine storage and recycling. Mutations in this gene result in α-synuclein proteins that can polymerize and aggregate into fibrils, and these aggregates are a major component of LBs.[55] Mutations in the SNCA gene also correlate to an earlier mean age of disease onset compared to other PD patients and a higher rate of dementia.[49] PARK2 codes for the parkin protein, and it is one of the largest known human genes, spanning more than 500 kb. Patients with a mutation in PARK2 have an earlier disease onset than other PD patients and a relatively slow disease progression.[55] It is thought that parkin aids in normal cellular protein degradation pathways. Without the parkin protein, other cellular proteins may not be degraded and removed from cells as efficiently as necessary, causing microtubule and mitochondrial dysfunction, and eventually cell death.[49]

The UCH-L1 gene codes for the ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) protein. Much like the parkin protein, UCH-L1 is thought to aid in protein degradation and clearance from neurons. Defects in the gene lead to protein accumulation and aggregation, including the UCH-L1 protein itself, which can also be found in LBs along with α-synuclein in PD patients.[55] As yet, no specific mutation has been linked between

the UCH-L1 gene and PD, despite extensive screening. For this reason, the UCH-L1 gene is indirectly related to the risk of developing PD.[49]

Much like mutations in PARK2 and the parkin protein, mutations in the autosomal recessive PINK1 gene result in an earlier onset of PD and a slow disease progression. However, having a single PINK1 mutation may predispose patients to have typical late-onset PD.[55] Phosphatase and tensin (PTEN)-induced putative kinase 1 (PINK1) is thought to regulate the electron transport chain in the mitochondria, a series of reaction used to generate cellular energy. In addition, PINK1 maintains the mitochondrial membrane potential as it pertains to programmed cellular death. Therefore, mutations in PINK1 lead to mitochondrial dysfunction and may lead to early cell death in neurons.[49]

The clinical phenotype associated with autosomal recessive DJ-1 is not well characterized due to its rarity, but it appears to be similar to parkin and PINK1 related parkinsonism. The gene codes for a protein ubiquitously found in mitochondria in brain tissue, and can aggregate with both parkin and α-synuclein when mutated. It normally protects against oxidative stress, regulates RNA-binding proteins, and prevents protein aggregation. Therefore, all of these processes are interrupted with DJ-1 gene mutations.[55]

Mutations have been found throughout LRRK2's gene domains, and despite the relatively uniform disease progression seen with those mutations, the neuropathology can vary greatly, even between family members carrying the same mutation.[49] LRRK2-related PD

often presents as a late-onset form of the disease. Leucine-Rich Repeat Kinase-2 (LRRK2) is found throughout the brain in the cytoplasm of cells, and functions as a kinase which interacts with the outer membrane of mitochondria. Mutations result in a dominant inheritance of the disease, perhaps through a toxic gain of function from increased phosphorylation on the mitochondrial membrane. LRRK2 protein interacts with the parkin protein, but not DJ-1, Tau, or α-synuclein.[55]

Gaucher's disease is the result of an autosomal recessive inheritance of a mutated glucocerebrosidase (GBA) gene. This disease state is characterized by lipid accumulation in bone marrow, lungs, spleen, liver, and sometimes the brain.[62] One rare manifestation of Gaucher's disease is early-onset parkinsonism.[55] Therefore, the GBA gene is considered a PD susceptibility gene. A study found 14% of PD carried mutations in this gene as compared to 5% of controls.[49] In fact, those people with a GBA mutation (with or without Gaucher's disease) are five times more likely to develop PD than those without the mutation.[63]

As stated before, PD was considered to be environmentally triggered until the last twenty years. Much is now known about the genetic aspects to PD, and studies continue to be performed in order to elucidate the gaps in knowledge. Recently, six new genetic risk factors of PD were identified by scientists in the National Institutes of Health (NIH).[64] Thanks to ongoing studies and the various animal models available,[65] the genetics surrounding PD can be analyzed, tested, and clarified.

Treatment

Since 1967, levodopa (L-dopa) has been a major medication for treating PD and remains the "gold standard" of treatment.[66] L-dopa is currently the most effective treatment for PD and is required by almost all patients as the disease progresses (refer to **Figure One** for levodopa's metabolism and the sites where certain therapies are active).[67] An early finding in the pharmacologic properties of dopamine is that it does not penetrate the blood-brain barrier, a highly specific mechanism inside the cranial blood vessels that only permit certain substances to reach the brain. In other words, dopamine cannot cross from the blood into the brain tissue where it is lacking in PD patients. However, its amino acid precursor (levodopa) can cross the barrier and enter the brain, where it is converted to dopamine via the enzyme *dopa decarboxylase*. This enzyme is found in other areas of the human body as well – the gastrointestinal tract, kidneys, liver, and other areas. This means that levodopa can be turned into dopamine in the blood before it crosses the blood-brain barrier, so less L-dopa reaches the brain. It can also result in high levels of dopamine in the blood, causing nausea and vomiting, and in some rare cases, cardiac arrhythmias and hypotension. To prevent this, L-dopa is combined with peripheral dopa decarboxylase inhibitors (DDIs), which would block the enzyme in all body locations except the brain. Not only does this reduce the side effects of L-dopa treatment, it also allows for smaller, but more effective, dosing regimens of levodopa. Due to the success of DDIs, L-dopa is only available in combination with a DDI. In the United States, the only approved DDI is carbidopa, although benserazide is available in other countries.[6]

Levodopa is a large neutral amino acid and is absorbed in the proximal small intestine by active transport. Therefore, the presence of other amino acids (from a patient's diet) will compete with L-dopa for absorption into the blood, and reduce the overall levodopa blood level. L-dopa also does nothing to protect the dying neurons, and therefore as PD continues to progress, there is a diminished capacity for neurons to store and convert L-dopa into dopamine.[66] This contributes to the appearance of motor complications that occur from prolonged use of L-dopa. These complications occur in 40% of patients after 5 years of therapy, and 100% of patients after 10 years.[67]

One type of motor complication is called "motor fluctuations". Motor fluctuations are the emergence of periods when PD symptoms increase despite L-dopa medication. It is not known whether these periods are caused by levodopa or are a consequence of disease progression.[6] The fluctuations are alternations between "on" time, when symptoms are controlled, and "off" time when the symptoms return. End-of-dose wearing off is the most common motor fluctuation, and occurs when a single L-dopa dose begins to wear off, and symptoms begin to return. This effect usually happens at predictable times. As the disease progresses, a longer period may be observed before a dose of levodopa begins to take effect, or symptoms may begin to reoccur earlier and earlier, or an "off" period may occur quickly and unexpectedly. Motor fluctuations are usually the most common reason for increasing the dose of L-dopa.[67]

Dyskinesia (coming from the root words for "difficult" and "movement") is a condition in which a person has involuntary, writhing movements, often described as choreiform.[6] These movements can involve the face, head, neck, arms, legs, torso, and respiratory muscles. The most common type of dyskinesia is peak dose, which occurs when L-dopa blood levels reach their highest concentrations. Less commonly, dyskinesia can occur when the effects of levodopa are beginning and/or when the effects are wearing off.[67] Dyskinesia can also take the form of painful muscle spasms known as dystonia. Dystonia occurs most often when drug levels are very low.[6] The ELLDOPA study in early PD patients suggests that higher doses of L-dopa lead to higher frequency of dyskinesia.[1] In this study, 30% patients on the highest L-dopa exposure (600mg) demonstrated wearing-off motor fluctuations and 16.5% developed dyskinesia in less than a year's time.[66] Recent human MRI studies in PD patients with dyskinesia have suggested neuro-anatomical changes in specific brain regions, particularly the frontal cortex. It is unclear whether these abnormalities are the cause or the result of dyskinesia, but further studies may link neuro-imaging with neuropathology and lead to the discovery of novel anti-dyskinetic treatments.[68]

L-dopa therapy should be started at the minimal effective dose and increased as necessary.[1] Carbidopa/levodopa is commercially available in tablet form as Sinemet, or as an orally disintegrating tablet as Parcopa, when swallowing becomes difficult (for these and all future drug information, please refer to **Table One**).[67] Orally disintegrating tablets have been shown to increase patient adherence to drug regiments, due to the ease

of drug administration.[69] This is important, as 8–11% of hospitalizations in elderly patients in the general population are attributable to non-adherence of their medication. Non-adherence is also associated with a twofold increase in costs of inpatient care. In particular, the consequences of non-adherence in PD include worse disease control, diminished mobility, greater fluctuations, dyskinesias, and worsening quality of life. Much like the general population, PD patients who do are non-adherers have significantly higher rates of yearly hospitalizations and a $3,451 yearly increase in medical costs as compared to medication-adhering PD patients.[70]

Another commercially available carbidopa/levodopa medication is Sinemet CR, an extended-release form of Sinemet. The extended-release provides a slower release of dopamine into the bloodstream, producing a longer duration of L-dopa's effects. L-dopa has a short half-life (about 90 minutes), thus requiring frequent medication daily. The extended-release form allows for decreased dosing frequency. However, this form of levodopa also takes longer to take effect after the first dose, thus forcing PD patients to endure their motor symptoms for more time initially (for example, when they wake up and all medication has worn off during the night) than the more immediate-release treatments.[6] In addition, the extended-release tablets have reduced bioavailability than the immediate-release forms, and less overall L-dopa enters the system.[1] Clinicians can use a combination of both immediate-release and extended-release L-dopa to achieve a sustained dopaminergic response.[69] In fact, a new PD drug was recently approved that

has both immediate-release and extended-release forms of carbidopa/levodopa combined in a single tablet (Rytary).

Other forms of levodopa may be available in the future. Gastro-retentive delivery systems, such as floating delivery systems or the so-called accordion pill (because it unfolds inside the stomach), will enable medication to remain in the stomach for extended periods of time, thus achieving sustained release of the medication and requiring less frequent dosing. There is a U.S. patent for an inhaled form of L-dopa which is being tested. Currently available in Europe and recently approved in the United States is a portable pump that delivers a gel formulation of levodopa/carbidopa directly to the duodenum, Duopa.[69] In other words, there is much research being performed to best introduce L-dopa into the body and enhance its medicinal effects. At the same time, medications and research to reduce the side effects of L-dopa (motor complications) are also being explored.

COMT (Catechol-O-Methyltransferase) inhibitors can be used in conjunction with levodopa/carbidopa in PD patients to lengthen L-dopa's duration of action.[71] This is done by blocking the COMT enzyme, which breaks down levodopa into 3-O-Methyldopa, homovanillic acid, or 3-methoxytyramine - waste products that are removed from the system.[67] Thus, L-dopa's half-life is extended and more is able to enter the brain from the blood.[71] Of the several types of COMT inhibitors, only entacapone and tolcapone have been studied in clinical trials.[72] The STRIDE-PD study, in which patients

were randomized to either levodopa /carbidopa or levodopa/carbidopa/entacapone, was performed to address the effects of entacapone. In this study, those exposed to entacapone exhibited a 30% increase in plasma L-dopa levels.[1] Both entacapone and tolcapone increase the "on" time of L-dopa medication and decrease the "off" time.[72] For this reason, COMT inhibitors are particularly helpful for people with motor fluctuations, as they reduce the wearing-off effect. On the other hand, COMT inhibitors may pose problems for patients with dyskinesia, especially if these symptoms occur at the peak of the levodopa dose.[6] There are other potential problems with COMT inhibitors as well. Tolcapone appears to be more potent than entacapone, most likely due to the fact that tolcapone can cross the blood brain barrier and block COMT in brain tissue, while entacapone cannot. However, tolcapone was observed to cause abnormal liver function that could result in death. For this reason, it was withdrawn from the market in Europe and Canada, and a black box warning was instituted in the United States.[73] Since then, the drug has been allowed to return in Europe, with more strict safety restrictions.[74] It is recommended that in patients taking tolcapone, liver enzyme testing should be every 2-4 weeks for the first six months, and then when clinically indicated after that.[67] Due to the success seen with COMT inhibitors, a triple combination of carbidopa/levodopa/entacapone (Stalevo) was created for patient convenience.[71]

Monoamine oxidase (MAO) plays an integral role in the metabolism of intra-cerebral dopamine, and inhibitors of this enzyme provide a therapeutic effect in PD patients.[75] Much like COMT inhibitors prevent the breakdown of L-dopa, MAO inhibitors prevent

the breakdown of dopamine.[67] The MAO enzymes are one of two subgroups – A or B. MAO-A inhibitors and nonspecific MAO inhibitors that inhibit both A and B types relieve depression by increasing the amount of dopamine and norepinephrine in the brain. Those patients taking these types of medications must adhere to dietary restrictions due to the "cheese effect". This "effect" is a phenomenon in which patients who ate foods rich in tyramine (such a red wines, chicken liver, and cheeses) experienced dangerous hypertensive episodes while taking nonspecific MAO or MAO-A inhibitors. However, MAO-B inhibitors are more specific and PD patients do not need to apply these dietary restrictions.[6] MAO-B inhibitors provide a modest symptomatic benefit in the treatment of early PD, weaker than the benefits seen with L-dopa or dopamine agonists. It is thought that MAO-B inhibitors may be best used in early stage patients with milder symptoms before using L-dopa medication.[76] In addition to the positive effects seen from MAO-B inhibitor therapy as they pertain to PD motor symptoms, there is also evidence that these treatments also improve cognition and executive functions in PD patients.[77]

There are two MAO-B inhibitors used in PD treatment, selegiline and rasagiline. Rasagiline is available in tablet form (Azilect). Selegiline is available in a pill form (Eldepryl) or in an oral disintegrating tablet (Zelapar).[67] There is currently a transdermal delivery of selegiline available to treat depression, but it is not yet indicated for PD treatment. However, an in vitro study exhibited promising results.[69]

Selegiline is a selective, irreversible MAO-B inhibitor, which forms a permanent covalent bond with the enzyme, and reversal of its effects requires the production of new enzymes.[75] As a single therapy, selegiline shows a modest symptomatic benefit for PD patients, and can delay L-dopa therapy. Combined with levodopa, selegiline can reduce motor fluctuations.[76] Side effects of selegiline usually include nausea, dizziness, hallucinations, and anxiety.[75] It was thought that treatment with selegiline leads to an increased mortality rate, but these concerns have been rejected based on large meta-analyses.[74] In animal models, selegiline blocks the ability of MPTP to cause parkinsonism. For this reason, it was thought that selegiline might posses some neuro-protective properties and therefore slow the progression of PD.[1] Therefore the DATATOP study was designed to determine selegiline's effects in early PD patients that have not yet begun L-dopa treatment. Due to selegiline's modest therapeutic effects, the group of patients taking selegiline exhibited better UPDRS scores than those in the placebo group.[75] However, follow-up studies and long-term studies revealed that selegiline has no neuro-protective effect.[6]

Rasagiline is also a selective irreversible MAO-B inhibitor that is prescribed alone or together with levodopa for PD treatment. It is considered that rasagiline is five times more potent than selegiline.[1] The higher potency suggests a greater symptomatic benefit, although studies claim them to be equally effective at treating PD in early stages.[78] Rasagiline reduces motor fluctuations and results in less "off" time from medication.[6] Side effects include dry mouth, headache, nausea, and abdominal discomfort.[75] Much

like selegiline, rasagiline was thought to be neuro-protective, and two studies, TEMPO and ADAGIO, were conducted to address this hypothesis. However, the results were not conclusive, and controversy still surrounds the neuroprotective benefit of rasagiline.[76]

Dopamine and dopaminergic drugs interact with one or more of the five known subtypes of receptors: D1, D2, D3, D4, and D5. These receptors are usually grouped into stimulatory (D1 & D5) or inhibitory (D2, D3, & D4) families. The efficacy of L-dopa is primarily due to the stimulation of the D2 receptors.[79] However, levodopa does not halt the progression of the disease, nor does it regenerate the neurons that have been lost. The dopaminergic neurons that degenerate during the course of PD are necessary to transform levodopa into its functional form, dopamine. As PD becomes more advanced, this process of converting L-dopa into dopamine becomes impaired. It is for this reason that dopamine receptor agonists are used. An agonist is a drug capable of combining with receptors and imitating the action of a neurotransmitter. A dopamine receptor agonist, therefore, mimics the activity of dopamine and relieves the symptoms of PD.[6] There are also several other advantageous aspects to dopamine receptor agonists. They work directly on the dopaminergic receptors without needing to be modified, released, or stored by the body. They have longer half-lives than L-dopa and produce more persistent stimulation than levodopa alone. Usually, dopamine receptor agonists are prescribed early in PD progression to postpone the onset of levodopa therapy.[80] This is particularly useful, as dopamine agonists can reduce or delay the motor complications associated with L-dopa therapy (motor fluctuations, and, to a certain extent, dyskinesias).[79] Despite this

advantage, it has been shown that levodopa provides more symptomatic benefit (based on UPDRS scores), and patients taking dopamine receptor agonists are also more likely to display dizziness, constipation, hallucinations, edema, and nausea. Depending on the dosage, dyskinesias can either be more pronounced or less pronounced with dopamine receptor agonist therapy.[81]

Pramipexole (Mirapex) is a dopamine receptor agonist with a high affinity for D2, D3, and D4 receptors. It has been shown in several clinical trials to decrease daily "off" time.[67] In addition to alleviating motor symptoms, some clinical trials have suggested pramipexole has also ameliorated depressive symptoms of PD. Also, some experimental models have shown some neuro-protective effects in animals, although this has not been reproduced in humans.[80] Pramipexole is available in a wide variety of dosage strengths, and is also available as an extended release tablet, so as to create a steady state of dopamine receptor stimulation. The extended release enhances compliance, but is also more expensive.[69]

Ropinirole (Requip) is a potent dopamine receptor agonist with high affinity for D2 and D3, and to a certain extent, D4. Clinical studies have shown the symptomatic effects of ropinirole in treating PD, however dyskinesias are more likely when compared to placebo, but not when compared to levodopa.[79] Much like pramipexole, some evidence of neuro-protection from ropinirole is exhibited in animal models, but has not been observed in human studies.[80] Also like pramipexole, ropinirole is available in many

dosage strengths, as well as an extended release tablet form. The extended release form, again, helps with adherence to medication regimens, but at a higher cost.[69]

Rotigotine (Neupro) is a dopamine receptor agonist with affinity for D2, D3, and some D1 receptors. What makes rotigotine different is its route of administration – a patch that is a transdermal system, delivering the drug through the skin throughout the day.[67] Data suggest that rotigotine can reduce "off" time during therapy, and can adequately treat the symptoms of PD like the other dopamine receptor agonists mentioned.[82] The patches also allow for dopamine receptor agonist treatment for those patients who have difficulty swallowing, which becomes more common as PD progresses.[79] Rotigotine was recalled by the FDA due to crystals that were forming on the patch, thus diminishing the overall drug being absorbed. This problem has since been addressed, and the patches are required to be refrigerated so as to prevent this crystallization. The patch is applied once daily to a different area of the body to prevent skin irritation at the site of the patch.[69]

Apomorphine hydrochloride (Apokyn), a non-addictive derivative of morphine, is a dopamine receptor agonist with high affinity for D2, D3, and D4 receptors.[79] The most rapid and effective route of administration of apomorphine is subcutaneous injection. It takes effect between ten and sixty minutes, and benefit can last up to two hours.[67] Many types of route of administration for apomorphine have been explored – sublingual, intranasal, pulmonary, and even rectal administration.[69] These pathways show some promise of behaving like apomorphine when it is injected subcutaneously.[79] In some

countries, apomorphine is also administered via a pump for continuous dopaminergic stimulation. The benefit of this pump system is a steadier stream of dopamine stimulation, thus eliminating the "on/off" phenomena, as well as eliminating the motor complications that accompany high levels or low levels of medication. This form of treatment has not yet been approved by the FDA for use in the US.[83]

There are some specific side effects associated with dopamine receptor agonists that require special attention. All dopamine receptor agonists are linked to some rare side effects: sleep attacks (falling asleep suddenly and without warning) and dopamine dysregulation syndrome. This syndrome is a severe impulse control disorder, and commonly includes compulsive or addictive gambling. Another potential side effect is restrictive valvular heart disease, in which the fibrosis (thickening) occurs in the circulatory system, thus creating problems with blood flow and potentially leading to heart failure. This condition is caused by ergot-derived dopamine receptor agonists. All the dopamine receptor agonists mentioned previously to treat PD are considered non-ergot derivatives, and therefore do not usually exhibit this potential risk. [74]

Amantadine (Symmetrel) has been used to treat PD for decades. Its therapeutic effects were first recognized when PD patients took it to guard against influenza and reported that their symptoms had lessened.[6] The mechanism of amantadine is unclear. It is thought that amantadine could trigger the release of dopamine-containing vesicles, thus promoting dopamine's effects. It could also inhibit dopamine reuptake, this prolonging

dopamine's effects. It is also possible that amantadine possesses dopamine receptor agonist activity.[84] Amantadine has been found to decrease dyskinesias in clinical trials67 and is particularly useful in early PD patients to delay the introduction of levodopa.[1] It can relieve symptoms of rigidity, slowness, and minor gait abnormalities.[6] In particular, amantadine has been shown to improve subject-reported freezing of gait, a major source of disability and increased risk of falls in the PD community.[85] There is also evidence that amantadine can potentially curb the impulse control disorders that are observed in those PD patients taking dopamine receptor agonists.[86] Common side effects of amantadine include dizziness, insomnia, anxiety, nausea, and vomiting.[67] Amantadine may also cause ankle edema, as well as cause a skin condition called *livedo reticularis*, which is characterized by blotchy, red skin.[6] At high dosages, it is said that amantadine can also cause visual hallucinations or confusion.[1] Very rarely, it has been observed that amantadine use has caused corneal edema.[87]

Before levodopa entered center stage to treat PD, several surgical methods were attempted to alleviate PD symptoms. In the late 1940s and early 1950s, there were several reports on the efficacy of two procedures that reduced parkinsonian tremors – pallidotomy and thalamotomy.[88] In a thalamotomy, a small region in the thalamus is destroyed; likewise, in a pallidotomy, portion of the globus pallidus is destroyed. While these two procedures did reduce the tremors and rigidity seen in PD, they did not address the progression of the disease, nor did it address the other disabling features, such as slowness or clumsiness of movement or walking difficulties.[6] With the discovery and

utilization of L-dopa in the 1960s and given their irreversible nature, surgical treatments were less utilized. However, with motor complications associated with L-dopa treatment, there is a renewed interest in surgical procedures.[88]

Deep Brain Stimulation (DBS) began in 1987, when the discovery that electrical stimulation of functional targets within the brain was able to mimic the effects of a lesion (like those seen in pallidotomy and thalamotomy procedures). The difference being, that DBS is reversible and adjustable. While the therapeutic mechanisms of the procedure are still unknown and somewhat controversial, DBS is an effective therapy for a variety of neurological disease, including PD.[89] An electrode is surgically placed into the brain and connected to a pulse generator. The generator is the power source or battery of the system and is usually placed in the chest just beneath the skin.[67] Once the power source is implanted, the patient can easily turn the stimulation on or off. When the stimulation is on, an electrical current passes from the electrode to the target region.[6] Hyperactivity of the subthalamic nucleus (STN) and the globus pallidus internus (GPi) is thought to be a manifestation of PD progression, and therefore, both of these areas are common targets for DBS.[89] The thalamus is also a potential target for DBS in PD, however it has not has not shown to significantly control motor complications like the other two potential targets.[67] STN and GPi DBS have both been shown in randomized controlled clinical trials to be superior to medicine alone. Patients experience more "on" time, less dyskinesia, and improved UPDRS scores, sleep habits, and overall quality of life.[88] Several studies have been conducted to compared STN and GPi DBS. In 2009, the NIH

COMPARE trial demonstrated equal motor outcomes of both procedures, and no significant differences in mood or cognition. If a medication reduction is desired, then STN DBS is likely to be preferred. Meanwhile, if dyskinesias or pre-existing cognitive issues are present, then GPi is the best choice.[90] However, with DBS also come certain risks or complications. As with any brain surgery, there is a risk for complications during the procedure including hemorrhages, confusion, or seizures. There is also the risk of device-related complications, including infections or malfunctions. The final complications come from the electrical stimulation itself, and while this may be the most debilitating, most are also reversible. Involuntary muscle contractions, abnormal eye movements, and dysarthria (motor speech disorders) are all potential side effects that can be reversed with slight alterations to the electrical stimulation.[91] DBS has also been associated with impulse control disorders (much like dopamine receptor agonists),[92] as well as social maladjustment and a potential increased risk of suicide.[93] In addition, certain symptoms such as gait imbalance, gait freezing, and difficulty swallowing – major disabilities in PD – are not statistically improved by DBS.[94]

A wide array of potential treatments is available for patients for PD. Determining which course of action is best depends on the individual patient's manifestation of PD symptoms and the best method to address his or her concerns.

Insurance

Health care, including medications, is expensive, and few individuals can afford to pay the full costs. Having health insurance allows for treatment without huge medical bills. Most Americans have private health insurance, or participate in public programs, such as Medicare or Medicaid. According to the 2013 census, 86.6% of Americans (271.4 million) had health insurance during 2013, and 13.4% of Americans (42 million) were uninsured. 64.2% of Americans (201.1 million) were covered by private health insurance, while 17.3% (54.1 million) were covered by Medicaid, and 15.6% (49 million) were covered by Medicare.[95] Medicaid usually provides health care for low-income children and families, and people with disabilities. Covered services usually include doctor visits, hospital care, prescription drugs, and preventative care for children, among others. Medicare helps to pay for care in hospitals, nursing facilities, hospice care, and sometimes doctors' services and prescription drugs.[96] Many Americans are uninsured due to finances or pre-existing conditions, but Massachusetts is in a unique position because a health care reform bill was enacted within the state in 2006. It mandated that residents have health insurance or pay a non-compliance fee, it made health insurance affordable, and it improved the market for non-group insurance through reforms. The result of such a bill lowers out-of-pocket costs of health care and encourages the use of medical services more effectively and efficiently.[97] Despite these encouraging facts, disparities still exist between people who have private insurance and those who have public insurance, like Medicaid or Medicare. For example, patients on Medicaid had difficulty in accessing hand specialty care,[98] Medicaid patients were 22 times less like to

receive a liver transplant than similar patients with private insurance,[99] and children with public health care have limited access to surgical specialty when compared to similar patients with private health care.[100] PD patients with private insurance report significantly better quality of life and self-reported disability.[101] Disparities also exist within health care use among minorities as well.[102] Black patients with PD are significantly more likely to use Medicaid, and it has been shown that this community is at a systematic disadvantage of accessing Deep Brain Stimulation (DBS) surgery.[103] In addition, patients on public insurance plans, such as Medicare or Medicaid, and uninsured patients had significantly increased risks for postoperative complications within 30 days of neurosurgery.[104] Why does this disparity exist? It has been suggested that individuals with private insurance may possess better access to primary care, may pursue better health care options, and can more easily obtain preoperative and postoperative supports. In contrast, programs such as Medicaid are specifically designed for the low income population and predetermines that participants belong to lower socioeconomic groups than those in private health care systems. Another suggestion is the concept of health literacy, which is defined as the degree to which individuals understand basic health information and services. Low health literacy is more likely found in lower socioeconomic groups and in the elderly – the vast majority of both of these groups are insured by Medicaid and Medicare.[105]

Study Questions

It is the aim of this project to analyze the Parkinson's Disease and Movement Disorders Database in the hope of contributing to the background information and existing literature. This database is unique for several reasons. It is derived from Boston Medical Center, a hospital with a highly diverse patient population (refer to **Figure Two** for hospital racial demographics).[106] In addition, the database was begun after the implementation of "Romneycare," which required every resident of Massachusetts to have health insurance by law. While several studies have compared patients with insurance to those without, this database uniquely allows for the comparison between private insurance and public insurance. The database also contains large amounts of information regarding disease severity, medications, and complications. For these reasons, the Parkinson's Disease and Movement Disorders Database has important information to contribute to the understanding of PD as it pertains to race, sex, and insurance status.

SPECIFIC AIMS

The purpose of this study is to analyze the Hoehn and Yahr (H&Y) scores of patients both ON and OFF medication, a method of ranking and analyzing disease severity in Parkinson's patients. The hypothesis of this study is that the H&Y scores are impacted by race, gender, and insurance status. It is predicted that H&Y scores are lower in Caucasian than in other racial categories. There is no consensus on whether women or men have higher H&Y scores, so one hypothesis is just as valid as the other. It is also expected that those with private insurance will have lower H&Y values than those with public insurance. The patient population was culled from the Parkinson's Disease and Movement Disorders database associated with the neurology clinic at Boston University Medical Center. Data was gathered via a survey and included information pertaining to demographics, medications, side effects, family history, and other key parameters. The specific aims were to:

1) Perform a univariate analysis of study variables (gender, race, and insurance status) and potential confounders (age, education, and the years between onset and enrollment into the database) as each pertains to the H&Y scores ON and OFF medication
2) Perform a multivariate analysis of gender, race, insurance status, and confounding variables to determine the independent effects on H&Y scores ON and OFF medication
3) Perform a secondary analysis of gender, race, and insurance status as each pertains to common side effects of disease progression and treatment, including: compulsive behavior, hallucinations, dyskinesia, motor fluctuations, dementia, orthostatic hypotension, depression, freezing, psychosis, and other autonomic dysfunctions

These questions will elucidate the clinical features of PD patients from a highly diverse patient population. In addition, the analysis of the effect of public insurance versus private insurance has not yet been analyzed in the established literature.

METHODS

Patients and Database

Patients were recruited from a movement disorders clinic in the neurology department at Boston University Medical Center (BUMC) in Boston, Massachusetts between the years 2007 and 2012. Patients were eligible if they were diagnosed with a movement disorder (PD, essential tremor, and others) by a movement disorder specialist in the clinic. New patients, as well as patients that were already being treated by a neurologist at the clinic, were eligible for the study. Patients were treated by the movement disorder specialist, relevant information was gathered, the specialist filled out the survey form (to be discussed in the following section) while referring to medical records to verify information, and the subjects were then entered into the Parkinson's Disease and Movement Disorders Database, along with the Hoehn & Yahr (H&Y) score, both ON and OFF medication. There are 673 subjects in the Movement Disorders database. Only those diagnosed with PD were included in the analysis, a total of 452 subjects. To ensure confidentiality, the database used was de-identified, lacking the subjects' names and any other identifying information. The database was saved on a password-protected data stick, and the electronic file was itself password protected. The Institutional Review Board (IRB) at BUMC designated an exemption status for this project because of the steps taken to ensure confidentiality.

Survey Content

The survey contains questions regarding demographics, family history, disease category, medications, and surgical history. First, the subject's full name (omitted from the de-identified database), date of birth (month and day were omitted), address (omitted), primary language, and insurance provider were all reported. Then, a racial category was chosen that best reflected their background, their education level was identified, and their occupational background was indicated. The date at which the disease began to manifest itself (date of onset) and the date when the formal diagnosis of a movement disorder was made (date of diagnosis) were listed. Any related diseases diagnosed in their parents, grandparents, siblings, and children, as well as their own current diagnosis (or diagnoses) were included. These types of diagnoses included forms of dementia, types of dystonias (sustained muscle contractions), and other neurological disorders. Then, it was indicated which (if any) complications of the disease or treatment were experienced. These complications include compulsive behaviors, dyskinesia, dementia, depression, freezing, hallucinations, motor fluctuations, orthostatic hypotension, psychosis, or any other autonomic dysfunction. Finally, any therapeutic surgical treatments the subject had undergone, as well as current and past use of medications, were recorded. These medications could be specific to the treatment of the movement disorder, or they could be of more general use, such as antidepressants or anti-inflammatory agents.

Statistical Analysis

All statistical analyses were performed using JMP version 11.0.0. As with any database, there are times when information is missing and the field in the database is left blank. If data was missing, then JMP excluded that data point from that particular statistical analysis. Due to small numbers in certain racial categories, some were combined to enable statistical analysis. African – Black (Sub-Sahara), African North (Sahara or Northern Regions: Algeria, Egypt, Morocco, Tunisia, Etc.), and American – Black (African descent, originating in: Canada, Caribbean, Brazil, US, etc.) were combined into the racial group Black or African. Spanish (Cuban, Iberian Peninsula, Mexican, South or Central American, or Other Spanish Origin) was renamed Hispanic. The distinction between white Hispanic and black Hispanic is not addressed in the survey content, and therefore cannot be analyzed in this statistical analysis. The Caucasian category was maintained. All other racial groups were combined into the category "Other", due to the small number of patients within each category. Likewise, there were only four patients that were classified as Self-Pay under insurance classification. These four patients were combined with patients under public insurance, since it is likely that these patients had no health insurance when they arrived at the neurology clinic, and possibly, were then enrolled in some form of public coverage. It is also possible that these self-pay subjects paid cash for treatments because they are from a different country and aren't eligible for insurance in Massachusetts.

The association between H&Y ON and OFF medication with gender, race, and insurance classification were examined using univariate analyses. To test for differences between the means, a Student's t-test was used for gender and insurance status, since both categories only contained two factors. For race, which contains four factors, a One-way ANOVA was used, and if there was statistical significance, it was followed by the Tukey-Kramer test for individual pairs. Education level, a potential confounder, was also analyzed using a One-way ANOVA, followed by the Tukey-Kramer test if statistical significance was reached. Two other variables were analyzed as known confounders. One is age, and the other variable is the amount of time (in years) between the onset of PD and enrollment into the database (onset information). Both were analyzed via a regression model. Age and onset data, as known PD confounders, were also analyzed as each pertains to gender, race and insurance status. Much like the primary outcomes, race and education level were analyzed via a One-way ANOVA, while gender and insurance status were analyzed using a Student's t-test. This analysis was performed to address what confounding effects there variables had (if any) on gender, race, and insurance status.

A multivariate regression model analysis was run with the H&Y ON and OFF medication values as outcomes, and gender, race, age, years between onset and enrollment, and finally insurance status as predictors. After it was determined that education was not a confounder, it was excluded from all further analyses. Due the large number of subjects

excluded in this analysis (89 subjects are missing onset data), the regression models were run again, excluding this confounder.

The secondary outcomes of disease and treatment complications are dichotomous outcomes, classified as either being present or absent. Therefore, the associations with gender, race, and insurance status were examined via Chi-square tests. Some complications did not have sufficient numbers to accommodate a valid Chi-square analysis – these were not pursued in further analyses. For any complication with a statistically significant Chi-square value for any predictor, a logistic regression model was run for that complication that included gender, race, age, and insurance status. Onset data, lacking a large number of subjects due to missing data, was excluded form the logistic regression analysis. Education was also not included due to the determination that it was not a confounder. Odds ratios, confidence intervals, and p-values were calculated from this analysis.

RESULTS

Primary Outcomes

The demographics of the study population listed 57.7% of the population as male, and 58.0% of the population had public insurance or self-pay. The ages of the subjects reflected a normal distribution, with 93.36% of subjects falling between the ages of 50-89, and 62.83% of the subjects between the ages of 60-79 (**Table Two**). The mean age was 68.4 years with a standard deviation of 10.5 years. As described in the Methods section, the racial categories as they appeared on the survey (**Table Three**) were combined to form the new categories (**Table Two**). 83.0% of the subjects in the population were Caucasian, and the next biggest category was Black or African making up 6.2% (**Table Two**). The education level of this study sample was slightly skewed, with 50.7% having a college degree or higher (**Table Two**). Finally, the variable of "years between onset and enrollment" had a very wide range (0 – 40 years), but over half the subjects fell between zero and ten years in this category. Only 2.43% of subjects had 26 years or more between onset and enrollment (**Table Two**). The mean amount of time between onset and enrollment was 9.4 years with a standard deviation of 7.0 years.

Missing data was present for each study variable, but was between 1-2% in half of the variables. For insurance status, 10.2% of subjects had missing data. Under education, 16.2% of subjects had no data listed. Finally, under "years between onset and enrollment", 19.7% of subjects had missing data (**Table Two**). Missing gender data was sprinkled amongst the racial groups and was not specific to one category. In addition,

missing race information was approximately equal between males and females (**Table Four**). Missing gender information was split between those who also had insurance information missing and those with public insurance or self-pay. There were slightly more men with missing insurance information than women (**Table Four**). Missing race information was approximately equal between private insurance and public insurance and self-pay. Of the 46 subjects with missing insurance information, 41 of them were Caucasian (**Table Four**).

A univariate analysis of gender, race, insurance classification, education, age, and "years between onset and enrollment" as they pertain to both H&Y scores ON and OFF medication (the two primary outcomes) was performed (**Table Five**). The H&Y score ON medication was statistically significant to onset data according to the regression model run (p-value 0.008), which indicated that as the time from onset increases, the H&Y score ON medication also increases. However, it was not significantly related to any of the other variables according to the student's t-tests or the ANOVA analyses. The H&Y score OFF medication was significantly different between insurance categories (p-value 0.0003) with a mean public and self-pay score of 2.42 compared to the mean private insurance score of 1.92. Likewise, the H&Y score OFF medication was significantly different between genders (p-value 0.003), with the females scoring 2.45 and the males scoring 2.07. Both age and time from onset reached statistical significance in the H&Y score OFF medication (both p-values 0.0001). As both of these variables increase, so does the H&Y score OFF medication. Education did not reach statistical

significance in any category and thus was determined not to be a confounder. Education was excluded from subsequent analyses.

Age and onset information, determined to be confounding effects based on the univariate analyses, were analyzed as each pertains to the other variables (**Table Six**). Age was seen to be significantly different between insurance classifications (p-value 0.0001). Subjects with private insurance were 11 years younger than patients with public insurance, on average. Onset data was also significantly different between insurance classifications (p-value 0.005). The average amount of time between onset and database enrollment of patients on private insurance was 7.8 years, while for the subjects with public insurance it was an average of 10.0 years. There was also a significant difference between onset and enrollment between races (p-value 0.03), as it was 9.7 years on average in Caucasians and 5.7 years on average in Black or African patients. A regression model analyzing onset data and age yielded a p-value of 0.0001. As the time between onset and enrollment increased, the subjects were likely older at enrollment, and the age was increased.

A multiple regression analysis was performed on H&Y scores ON and OFF medication, taking into account gender, age, race, insurance status, and "years between onset and enrollment" (**Table Seven**). Despite significance seen in the univariate analysis, both gender and insurance classification were not seen to contribute significantly to the H&Y score OFF medication (p-value for gender 0.10; p-value for insurance classification 0.71).

Age contributed significantly (p-value 0.0003) as did the "years between onset and enrollment" (p-value 0.0001). As both of these variables increase, so does the H&Y score OFF medication. Despite no significance in the univariate analysis, there was significance under the racial categories. Black or African patients were 0.46 points higher when compared to Caucasian patients controlling for all the other variables (p-value 0.03). When analyzing the regression model of H&Y score ON medication, only "years between onset and enrollment" reached statistical significance (p-value 0.02). As the time between onset and enrollment increases, so does the H&Y score ON medication. This variable is the only one contributing to the H&Y score ON medication outcome, according to the statistical analysis.

A large number of subjects were excluded from the multiple regression analysis due to missing data under the category "years between onset and enrollment". A second round of multiple regression analyses was run for H&Y scores ON and OFF medication without this variable included (**Table Eight**). Age was shown to still be a contributing factor to H&Y scores OFF medication (p-value 0.0001), increasing the score 0.04 points per year. Race was not statistically significant in any category (p-values 0.83, 0.81, and 0.46 for categories Black or African, Hispanic, and Other respectively as compared to the reference category, Caucasian). There was still no significant statistical contribution from the insurance classifications either (p-value 0.62), despite the significance seen in the univariate analysis. Gender was seen to be statistically significant (p-value 0.01), with an H&Y score 0.16 points higher in women as compared to men. The multiple

regression analysis performed on the H&Y scores ON medication likewise took into account gender, age, race, and insurance status. None of these factors reached statistical significance.

Secondary Analysis

The univariate relationship of several PD complications as they relate to gender, race, and insurance status were analyzed (**Table Nine**). Significant statistical differences between genders were observed in the following complications: dyskinesia (p-value 0.0001), motor fluctuations (p-value 0.0007), and freezing (p-value 0.006). Women had more dyskinesia and motor fluctuations than men, while men had more freezing than women. Significant statistical differences between insurance categories were observed in the following complications: hallucinations (p-value 0.001), dyskinesia (p-value 0.04), dementia (p-value 0.001), and other autonomic dysfunctions (p-value 0.02). The percentage of subjects with public insurance or those who self-pay was higher for each of these complications than the percentage of subjects on private insurance. There was no statistical significance between racial categories for any of these complications.

Multiple logistic regression analyses were performed on each complication that displayed a statistically significant p-value in any of the three variables analyzed via Chi-square test (**Table Ten**). Hallucinations, which only had significance between insurance categories, was an effect of age (p-value 0.0004, odds ratio: 1.05), rather than insurance (p-value 0.28). As age increases, so does the likelihood of experiencing hallucinations.

The regression model of dyskinesia showed statistical significance between genders (p-value 0.0001). The odds ratio was 2.35 in this analysis, meaning women were more likely to have this complication. Insurance classifications also reached significance for the dyskinesia logistic regression (p-value 0.03), and the odds ratio was 1.75. This indicates subjects on public insurance and self-pay are more likely to experience this complication than subjects on private insurance. Finally, the odds ratio was 0.23 for the Black or African category as compared to the Hispanic racial category (p-value 0.03) for dyskinesia. Black or African patients, therefore, are less likely to experience dyskinesia than Hispanic patients.

Motor fluctuations, which were only statistically significant between genders in the Chi-square analysis, were still significantly different between both genders (p-value 0.007) and had an odds ratio of 1.76. Like dyskinesias, females are more likely to experience motor fluctuations than males. Insurance status was statistically significant in the motor, meaning people with private insurance are less likely to experience motor fluctuations. Age also had a modest, but statistically significant contribution to motor fluctuations (p-value 0.05), with an odds ratio of 0.98. This means that the likelihood of experiencing motor fluctuations actually decreases with age.

The regression model for dementia displayed significant p-values for age (p-value 0.0002) and a modest odds ratio of 1.06. Similarly, the category of "other autonomic

dysfunction" had an effect of age (p-value of 0.05) and minor odds ratio of 1.03. As age increases, so does the likelihood of experiencing dementia and some "other autonomic dysfunction." There was statistical significance between genders (p-value 0.03) for dementia, and an odds ratio of 0.55. Likewise, there was also a difference between genders in the category "other autonomic dysfunction" (p-value of 0.04) and an odds ratio of 0.55 comparing females to males. Women are less likely to experience dementia and other autonomic dysfunctions than men.

The freezing complication had several significant comparisons. Gender (p-value 0.01) had an odds ratio of 0.49 comparing females to males, indicating women are less likely to experience freezing. Age (p-value 0.02) had an odds ratio of 1.04. As age increases, so does the likelihood of experiencing freezing. Finally, there was some significance between racial comparisons: Caucasian as compared to Other (p-value 0.02) had an odds ratio of 0.25, and Black or African as compared to Other (p-value 0.03) had an odds ratio of 0.20. Therefore, both Caucasians and Black or African subjects are less likely to experience freezing than the subjects included in the Other racial category.

DISCUSSION

This study attempted to analyze demographic information and its relationship to PD. The variables of interest were gender, race, and insurance classification. The primary outcome of this study was the Hoehn and Yahr (H&Y) scoring system – a method of ranking the PD progression in a patient. The H&Y scoring system is mostly whole numbers that rank disease progression, and are major milestones in PD. The exceptions to the whole number ranking system are the values 1.5 and 2.5, which were added to the original scale to address some symptoms not originally included in the 1967 system and paper. For this reason, a half-stage change can be considered clinically significant. Education level was addressed as a possible PD predictor, but was excluded after observing no significant contributions following the univariate analysis. Age and "years between onset and database enrollment" were included in analyses as confounders. Some analyses excluded onset data due to high numbers of missing data.

Race

Despite the highly diverse patient population at BUMC (**Figure Two**), the study population has an overwhelming number of Caucasians. It has been reported that this racial group has a higher incidence and prevalence of PD than other racial groups. While it is unsurprising to have a larger Caucasian population, the large disparity seen in this population is striking, and may affect the power of the analyses. In addition, studies have displayed similar incidence and prevalence data in the Latino community and Caucasians.

Due to this information, it was expected that the Hispanic racial category was to be larger.

It has been demonstrated that black PD patients exhibit greater disease severity and disability than Caucasian PD patients. Surprisingly, the results of the univariate ANOVA analyses yielded no significant differences between racial categories in either of the primary outcomes (H&Y ON and OFF medication). However, in the multivariate regression analysis, Black or African PD patients are 0.46 points higher on the H&Y OFF medication scale than white patients. Advancing from one H&Y stage to the next is considered a disease progression of major clinical significance. Therefore, black subjects are half a stage ahead of white subjects in disease progression, while all the other variables are held constant. It has been thought that this disparity seen between black patients and Caucasian patients was due to under-reporting of symptoms and, as a result, delayed treatment. However, this analysis rejects this possible explanation. According to the onset data, Black or African patients are enrolled into the database sooner than any other racial category following disease onset. This means that delayed treatment is no longer a viable explanation. To further prove this point, when onset data is excluded from the regression analysis, the statistical significance seen in the racial categories disappears. Therefore, a different explanation is needed to explain this disparity. It could be the result of overall poorer health in the black community. It is known that minorities are usually of a lower socio-economic class than white communities, and therefore may not be able to afford lifestyles choices that improve overall health, resulting in a higher

H&Y score. Also, co-morbidities are more common in black PD patients and this may affect the overall H&Y score.

The Hispanic and Other categories are not statistically significant in this analysis. This may be the result of a lack of power in the analysis, derived from the small number of subjects in both of these categories. In addition, the Other category includes various racial categories, and any effect of one group may be masked by the presence of the others. On the other hand, there may be no real difference in these groups as compared to Caucasians, and there is nothing in the literature to cast suspicion that there should be.

Both analyses run for H&Y scores ON medication yielded no statistical significance for any race category compared to Caucasians. This indicates that the study sample is adequately medicated to address PD symptoms and progression, and that no one racial group has a statistical benefit or detriment over any other. Thirteen subjects had missing racial data and were excluded from any analysis including race. Due to the small numbers of minority subjects, these data points could have some unknown impact on the data, but with the overwhelming number of Caucasians in the study sample, this is unlikely.

Gender

There are slightly more men than women in the study population, but this was expected because it is reported that men are more likely to develop PD than women. Only seven

subjects were missing gender data, and given the high numbers of both men and women, this statistic is not considered detrimental to the study.

In the univariate analysis, women have a greater disease severity that is statistically significant for the H&Y score OFF medication. In the two multiple regression analyses run for H&Y scores OFF medication, gender takes on different statistical values. When including "years between onset and enrollment", there is no statistically significant difference between the sexes. Excluding onset data and including more subjects, gender becomes statistically significant. The question of which analysis to believe is a moot point. In the analysis excluding onset information, women are higher than men by 0.16 points, but this value, which is statistically significant, is not of clinical significance. If two patients differed by 0.16 units in the H&Y scoring system (which would be impossible to measure or determine) then both patients would most likely be grouped into the same whole number ranking system and be deemed clinically equivalent. For this reason, differences between H&Y scores OFF medication between genders may be deemed clinically insignificant. With the varying claims found in the literature regarding disease severity between genders, there was no clear hypothesis as to the difference between H&Y scores OFF medication.

Both analyses run on H&Y scores ON medication did not result in statistically significant differences between genders, thus indicating that men and women, overall, are appropriately medicated to treat PD symptoms.

It is believed that men are more likely to exhibit some symptoms of PD, and others are more common in women. While there is no clinical difference overall between genders according to the regression analyses, this does not indicate that PD is the same between them, or that men and women are experiencing PD in the same way. The H&Y scoring system is simply not designed to address these subtleties in disease manifestation.

Insurance

There were more subjects on some form of public healthcare or were considered self-pay at the time of their enrollment than those who had private insurance – from the patient population from which subjects were culled, this data is not surprising. Unfortunately, 46 subjects were missing insurance information, which makes up over ten percent of the overall subject population. These 46 subjects were excluded from any analysis in which insurance information was analyzed, and may have impacted the results, had they been included.

In the univariate analysis, the H&Y score OFF information was significantly higher in those subjects with public insurance or who were classified as self-pay. According to the regression analysis, the H&Y score OFF medication was not observed to be statistically significant for insurance classification. The statistical significance seen in the univariate analysis is therefore a confounded effect due to age and onset data. Both of these confounding factors are greater in the public insurance or self-pay category as compared to the private insurance category. As with the other variables, in both the univariate and

the multiple regression models of the H&Y score ON medication, insurance is not statistically significant at impacting the score.

There is no reason to believe that insurance status will impact the disease progression of PD. Instead, insurance status may reflect the treatment options available and the efficacy of therapy, which is then expressed in the H&Y score. Subjects with private insurance possess better access to primary care and pursue better health care options. These factors would suggest PD patients with private insurance should also have lower H&Y scores due to improved monitoring and treatments. In addition, patients with public insurance are thought to belong to lower socioeconomic populations, which are known to possess lower health literacy. Better health literacy translates to better overall health, which also should result in lower H&Y scores. For these reasons, it was thought that both H&Y scores both ON and OFF medication would be lower in private insurance as compared to the public insurance classification.

There have been no prior studies performed that compare PD patients with private insurance to those with public insurance – this study is the first to do so. In this study population, there is no difference between the insurance classifications in terms of H&Y scores. This may be due to the possibility that the H&Y is not sensitive enough to detect differences between these two groups. Another possibility for this lack of a significant difference is the homogeneity of the study sample. In addition to the lack of racial diversity, the education demographics inform us that the study population is surprisingly

educated, with half of the sample having a college degree or higher. This begs the question of whether this study population accurately represents the background insurance populations. On the other hand, this lack of significance may be a true effect, and there could be no difference between patients with public or private insurance.

Age and Onset Data

Much like the other variables, age is not statistically linked to H&Y scores ON medication. Regardless of a subject's age, their respective treatment appears effective at treating PD symptoms. Age is statistically significant in both regression analyses run on H&Y scores OFF medication. This is unsurprising, as age is a known predictor of PD, and has some confounding effects in the analyses run. Despite the statistical significance, the clinical significance of age is minimal. The effect of each individual year shows a rise in the H&Y score of 0.04 units, and therefore a decade would display an increase of 0.4 units in the H&Y score OFF medication. A PD patient will spend an average of two to three years per H&Y stage. Therefore, the effects due to age are small and the clinical implications are minimal.

Onset data significantly impacts both H&Y outcomes in the univariate analyses. Earlier onset would suggest a longer disease duration, which would be reflected in the PD progression and subsequent H&Y score. Therefore, onset data is a PD predictor, and was included in the regression analyses as a confounder. Onset data is statistically significant not only for H&Y scores OFF medication, but it also is the only variable to be

statistically significant for H&Y scores ON medication. However, much like the age data mentioned above, the clinical significance of its contribution to these scores is minimal.

Despite the lack of clinical significance seen in this study with regard to age and onset data, a different study design would better address the clinical importance of these variables. A cohort study design could determine the effect of age or onset over a period of time within subjects.

Secondary Analysis

Following the Chi-square analyses, only six complications reached significance after excluding any analyses with insufficient numbers. In the logistic regression analyses performed on these six complications, onset data was not included due to high numbers of subjects that would be excluded. Given the small prevalence of some of these complications in the study sample, it was thought that including as many as possible would make for a better secondary analysis.

Age was statistically linked to hallucinations, motor fluctuations, dementia, freezing, and other autonomic dysfunction – five out of the six complications. According to the logistic regression, motor fluctuations are actually seen to decrease per year, which is seen clinically. The other four complications are all observed to increase over time during PD progression. According to the literature, disease complications are more likely

as PD continues to progress, and therefore may be associated with age, but they are not considered to be caused by aging.

Insurance status exhibited some significant odds ratios as well. Those subjects with public insurance had an increased odds ratio of 1.75 for dyskinesia and 1.85 for motor fluctuations than subjects with private insurance. Dyskinesia and motor fluctuations coexist clinically, so it is not surprising to find significance in both of these complications simultaneously. They are both reflections of levodopa dosage and duration of PD. This may indicate that levodopa dosage is not as closely monitored in public insurance as compared to private insurance. Subjects on private insurance may also have more options to help adjust L-dopa dosage, and better coverage for adjunct medications to reduce the frequency of these complications. Conversely, these effects may be the result of onset data, which was excluded from the secondary analysis.

Gender is highly significant in the secondary analyses, reaching statistical significance in five out of the six categories. Based on the odds ratios, women are 2.35 times more likely to experience dyskinesia than men, and 1.76 times more likely to experience motor fluctuations. In the literature, dyskinesias are more prevalent in women, and as stated above, dyskinesia and motor fluctuations clinically coexist, so these findings were expected. These statistics may indicate that females in this study sample have more difficulties with levodopa dosages than males. They may also suggest that women may require closer medication monitoring or more frequent levodopa dosage adjustments.

The odds ratios also state that men are 1.82 times more likely to have dementia than women, 1.82 times more likely to have some other autonomic dysfunction, and 2.04 times more likely to experience freezing than women (these values are the inverse of the odds ratios calculated from the regression models). There are several issues that fall under the category "other autonomic dysfunction" – constipation, urinary frequency, and sexual dysfunction. Sexual dysfunction is more commonly found in males than females, and it may be this condition that causes the statistically significant prevalence in males over females. On the other hand, constipation is more common in women in PD. Without more information regarding the specific autonomic dysfunctions, no definite conclusions can be drawn. There is no previous information in the literature regarding freezing of gait or dementia as they pertain to gender. Both of these complications are considered part of PD progression. According to the primary regression analyses, gender does not differ significantly regarding H&Y scores, and therefore doesn't differ significantly in terms of PD progression. For this reason, it is surprising that dementia and freezing differ between sexes. This data could indicate that some other factor not analyzed in this study is a risk factor for these complications, and that the H&Y scoring system is not designed to address dementia in the progression of PD. In addition, these complications could be affected by other medications being taken along with L-dopa, which are not addressed in this study.

There are also some racial comparisons that reach statistical significance. The Hispanic category has an odds ratio of 4.35 as compared to the Black or African category in

experiencing dyskinesia. There are no previous studies that have addressed this or any other complication between the Latino community and the black community. While this effect may be real, there are some points to consider. Given the small number of subjects in both of these categories, there is reason to suspect the power of this analysis may be lacking. Also, the Black or African category was the only racial group to reach clinical significance of a higher H&Y score. For this reason, it isn't expected for this racial category to show significantly less dyskinesia, a complication believed to be associated with PD progression. Finally, dyskinesia and motor fluctuations coexist clinically, and to see a significant effect in one without the other is unexpected.

For the freezing complication, the Other racial category has an odds ratio of 4.00 compared to Caucasians and has an odds ratio of 5.00 compared to the Black or African category. Again, given the small number of subjects in the racial category Other, the power of the analysis may not be sufficient to encourage much trust in these values. In addition, the Other category which reaches significance in the freezing complication, is made up of a variety of racial backgrounds, and no meaningful conclusions can be drawn from it.

Limitations and Future Directions

There are several limitations to this study. The first limitation is the issue of race. The study population is almost 83% Caucasian and limits the generalizability of this study. It also reduces the power of the racial analyses. In addition to this, there is a problem with

the way the Latino community is reported. It is likely that white Latino patients and black Latino patients were combined under the Spanish (renamed Hispanic) category, when they should have been separated based on their racial background. This results in a mixing of racial categories, and does not accurately represent a portrait of the study population. Given the small number of subjects in the Spanish category, it is unlikely that this mixing of racial backgrounds has a profound effect on the results. More importantly, the racial information of this study sample lends credence to the role of genetic background to the prevalence of PD. Prevalence cannot be tested in this study sample, but taking into account the highly diverse racial background from which it is drawn (**Figure Two**), one would expect a highly diverse study sample. The fact that almost the entirety of this study sample is Caucasian implies a genetic influence in this study population.

Another limitation is missing data. Missing data impacts the study in two ways. The first is that missing data, obviously, cannot be included in an analysis and therefore may have some unknown impact on the results. However, subjects with missing data were totally excluded from regression analyses. These subjects could not contribute what information they did possess to the regression analyses, reducing the study sample further. Very few variables had large amounts of missing data – the exceptions being insurance data and onset data. To combat missing onset data, the regression analyses of H&Y scores were run twice, including and excluding this data. Missing data is common in any database,

but perhaps there would be less if subjects filled out the survey themselves, instead of the specialists doing so on the subjects' behalves.

Another limitation is the usage of H&Y scores instead of the UPDRS. As mentioned earlier, the H&Y scoring system is a series of ranks based on PD progression. These ranks are single whole numbers, with the exceptions of 1.5 and 2.5. This type of scoring system, while useful for a quick analysis of PD, does not adequately address many of the subtleties of PD. The UPDRS, alternatively, is a method of ranking and addressing several aspects of PD including daily activities, mood, and quality of life, in addition to the motor symptoms. The UPDRS would have allowed for a study of greater depth and sensitivity, had it been available.

While these limitations present a real problem for the study, the study itself is scientifically sound, and accurately portrays the PD community from BUMC. The results attained tend to agree with the established literature, which encourages trust in the analyses.

Looking towards the future, this study highlights the information that is lacking in the database, and can encourage more thorough collection in the future. There is much information in the database that was not addressed in this current study – medication and family history, to name two examples. There are still many questions that can be asked from this database, and it has many pieces of information to contribute to the PD

community and to other movement disorders. The most immediate follow-up to this study would involve the collection of UPDRS scores. If they can be determined and recorded, UPDRS scores would allow for a more sensitive study, and may perhaps find statistical and clinical significance where there was little or none in this current study. They would also permit more specific questions to be asked – addressing topics such as mood, everyday activities, and quality of life, which all make up portion of the UPDRS. It is also necessary to delve further into the insurance information that is available. There was no statistical significance shown in this study, but with so little information known regarding PD in public versus private insurance, the Parkinson's Disease and Movement Disorders database offers a prime opportunity to investigate this comparison further. In particular, the medications that are available for private insurance as compared to public insurance could be analyzed and evaluated, along with complications or side effects that manifest within the groups.

Conclusion

Race, gender, and insurance status were all analyzed to illuminate what impact (if any) these variables had on the Hoehn and Yahr (H&Y) scoring system, both ON and OFF medication.

Despite significance seen in the univariate analysis, gender does not appear to have a significant relationship to the H&Y scores, according to the multiple regression model. However, this does not indicate that males and females experience PD in similar

manners. This point is strengthened by the secondary analysis, demonstrating dyskinesia and motor fluctuations as more likely in women, and freezing of gait, dementia, and other autonomic dysfunctions as more likely in men. Some complication disparities have been observed in the literature, but more research is needed to elucidate the cause.

Insurance status was also observed to have statistical significance in the univariate model, but not in the multiple regression analysis. Despite this lack of significance, more research is needed for verification in a more sensitive outcome measure, such as the UPDRS. Subjects on public insurance were more likely to experience dyskinesia and motor fluctuations which either indicate poorer L-dopa monitoring and dosage adjustment between these groups, or are the result of the confounding effects of onset data which was excluded from the secondary analysis. There have been no studies performed contrasting public and private insurance in PD – it is a comparison that should be addressed in future studies.

Racial categories exhibited no statistical significance in the univariate model, but in the multiple regression analysis, Black or African PD patients were found to be significantly higher in H&Y scores when compared to Caucasian subjects. This replicates established literature, but also addresses the current hypothesis behind this disparity. As demonstrated in this study, black subjects with PD had disease progression independent of disease onset and enrollment (treatment). Therefore, the notion that black patients

seek treatment later than white patients is not a valid explanation for this disease disparity. More research is required to discover the true cause.

APPENDIX

Figure One – Parkinson's Disease Medications

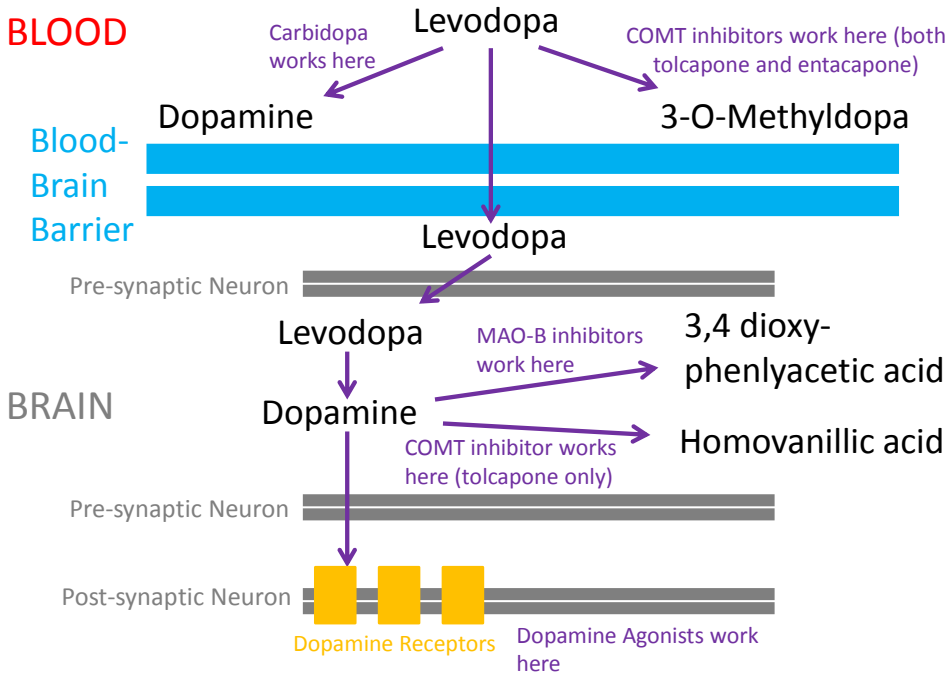

Figure Two – BUMC Hospital Racial Demographics

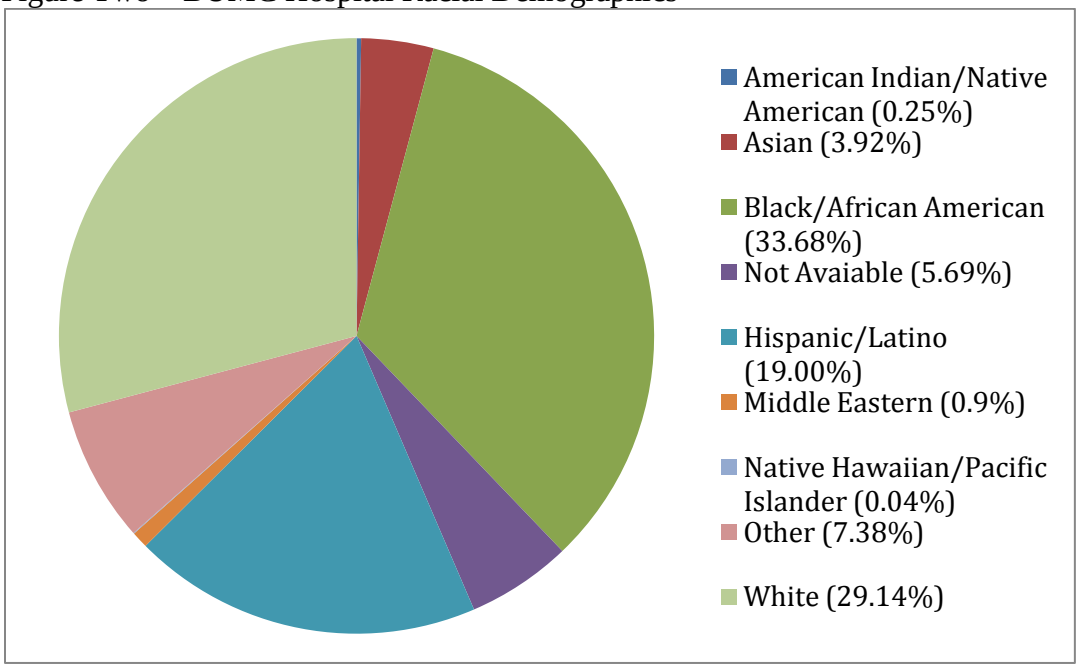

Table One – Parkinson's Disease Medications

Medication	Dosages (mg)	Route of Administration	Half-life	Type
Carbidopa/levodopa Immediate Release (Sinemet)	10/100, 25/100, 25/250	Tablet that is Swallowed	1.5 hours	L-dopa
Carbidopa/levodopa Extended Release (Sinemet CR)	25/100, 50/200	Tablet that is Swallowed	4-6 hours	L-dopa
Carbidopa/levodopa Oral Disintegrating (Parcopa)	10/100, 25/100, 25/250	Tablet that Dissolves on Tongue	1.5 hours	L-dopa
Carbidopa/levodopa Immediate and Extended Release (Rytary)	23.75/95, 36.25/145, 48.75/195, 61.25/245	Tablet that is Swallowed	2 hours	L-dopa
Carbidopa/levodopa Enteral Suspension (Duopa)	4.63/20 per 1 mL	Liquid that is Pumped into Small Intestine	1.5 hours	L-dopa
Carbidopa/levodopa /entacapone (Stalevo)	12.5/50/200, 25/100/200, 37.5/150/200, 50/200/200	Tablet that is Swallowed	1.7 hours	L-dopa/COMT inhibitor
Entacapone (Comtan)	200	Tablet that is Swallowed	2.4 hours	COMT inhibitor
Tolcapone (Tasmar)	100	Tablet that is Swallowed	3.5 hours	COMT inhibitor
Rasagiline (Azilect)	0.5, 1.0	Tablet that is Swallowed	3 hours	MAO-B inhibitor
Selegiline (Eldepryl)	5	Tablet that is Swallowed	2 hours	MAO-B inhibitor
Zydis selegiline HCL Oral Disintegrating (Zelapar)	1.25, 2.5	Tablet that Dissolves on Tongue	1.3 hours	MAO-B inhibitor
Ropinirole (Requip)	0.25, 0.5, 1, 2, 3, 4, 5	Tablet that is Swallowed	6 hours	Dopamine Agonists
Ropinirole Extended Release (Requip XL)	2, 4, 6, 8, 12	Tablet that is Swallowed	6 hours	Dopamine Agonists
Pramipexole (Mirapex)	0.125, 0.25, 0.5, 1.0, 1.5	Tablet that is Swallowed	8-12 hours	Dopamine Agonists
Pramipexole Extended Release (Mirapex ER)	0.375, 0.75, 1.5, 2.25, 3.0, 3.75, 4.5	Tablet that is Swallowed	8-12 hours	Dopamine Agonists
Apomorphine (Apokyn)	30mg per 3mL	Subcutaneous Injection	40 minutes	Dopamine Agonists
Rotigotine (Neupro)	1, 2, 3, 4, 6, 8	Transdermal Patch	5-7 hours	Dopamine Agonists
Amantadine (Symmetrel)	100	Tablet that is Swallowed	17 hours	Other

Information obtained from Medlibrary.org [107] and Parkinson.org [108]

Table Two – Study Population Demographics

Category	N	% of Total
Gender		
F	184	40.7%
M	261	57.7%
Missing	7	1.6%
	Mean	**SD**
Age (years)	68.4	10.5
Age	**N**	**% of Total**
20-29	1	0.2%
30-39	2	0.4%
40-49	14	3.1%
50-59	82	18.1%
60-69	131	29.0%
70-79	153	33.9%
80-89	56	12.4%
90-99	5	1.1%
Missing	8	1.8%
Race	**N**	**% of Total**
Black or African	28	6.2%
Caucasian	375	83.0%
Hispanic	17	3.8%
Other	19	4.2%
Missing	13	2.9%
Insurance Status	**N**	**% of Total**
Private	144	31.9%
Public and Self-Pay	262	58.0%
Missing	46	10.2%
Education	**N**	**% of Total**
< High School	17	3.8%
Some High School, no degree	14	3.1%
High School degree/GED	83	18.4%
Some College, no degree	36	8.0%
Associate degree	10	2.2%
Bachelor's degree	110	24.3%
Graduate or Professional degree	109	24.1%
Missing	73	16.2%
	Mean	**SD**
Years between Onset and Enrollment	9.4	7.0
Years between Onset and Enrollment	**N**	**% of Total**
0-2	50	11.1%
3-5	78	17.3%
6-10	106	23.5%
11-15	60	13.3%
16-20	43	9.5%
21-25	15	3.3%
26-30	6	1.3%
31-35	3	0.7%
36-40	2	0.4%
Missing	89	19.7%

Table Three – Racial Groups as they appear on Survey

Specific Racial Groups	N	% of total
African - Black (Sub-Sahara)	1	0.2%
African - North (Sahara or Northern Regions: Algeria, Egypt, Morocco, Tunisia, Etc.)	4	0.9%
American - Black (African descent, originating in: Canada, Caribbean, Brazil, US, etc.)	23	5.1%
American Indian/Alaska Native	6	1.3%
Asian - East (China, Japan, Korea, etc.)	9	2.0%
Asian - West (Bangladesh, India, Iran, Iraq, Pakistan, etc.)	2	0.4%
Caucasian	375	83.0%
Mixed Race	1	0.2%
Native Hawaiian or Other Pacific Islander	1	0.2%
Spanish (Cuban, Iberian Peninsula, Mexican, South or Central American, or Other Spanish Origin)	17	3.8%
Missing Information	13	2.9%

Table Four – Missing Data

	Female	Male	Gender Missing
Broad Race			
Black or African	15	13	0
Caucasian	146	226	3
Hispanic	10	6	1
Other	8	9	2
Race Missing	5	7	1
Insurance Classification			
Private	51	93	0
Public and Self-Pay	116	143	3
Insurance Missing	17	25	4

	Private	Public and Self-Pay	Insurance Missing
Broad Race			
Black or African	10	17	1
Caucasian	118	216	41
Hispanic	2	15	0
Other	10	7	2
Race Missing	4	7	2

Table Five – Univariate Analysis

	H&Y ON Mean (SD)	**H&Y OFF** Mean (SD)
Gender		
F	0.8 (1.5)	2.5* (1.3)
M	0.7 (1.3)	2.1* (1.4)
N excluded in analysis due to missing data	7	7
P-value from Student's T test	0.71	0.003
Race		
Black or African	0.9 (1.6)	2.4 (1.5)
Caucasian	0.7 (1.4)	2.2 (1.3)
Hispanic	0.6 (1.4)	2.2 (0.8)
Other	0.3 (0.8)	1.8 (1.2)
N excluded in analysis due to missing data	13	13
P-value from ANOVA	0.52	0.50
Insurance Classification		
Private	0.5 (1.1)	1.9* (1.1)
Public and Self-Pay	0.7 (1.5)	2.4* (1.4)
N excluded in analysis due to missing data	46	46
P-value from Student's T test	0.10	0.0003
Education		
< High School	0.7 (1.7)	2.8 (1.4)
Some High School, no degree	1.1 (2.0)	2.6 (1.7)
High School degree/GED	0.7 (1.4)	2.1 (1.2)
Some College, no degree	0.9 (1.4)	2.5 (1.2)
Associate degree	0.3 (1.0)	2.5 (1.4)
Bachelor's degree	0.8 (1.4)	2.2 (1.2)
Graduate or Professional degree	0.7 (1.5)	2.1 (1.3)
N excluded in analysis due to missing data	73	73
P-value from ANOVA	0.84	0.20
Years between Onset and Enrollment		
N excluded in analysis due to missing data	89	89
P-value from Regression Model	0.008	0.0001
Age		
N excluded in analysis due to missing data	8	8
P-value from Regression Model	0.38	0.0001

Table Six – Confounding Analysis

	Age (y) Mean (SD)	**Years between Onset and Enrollment** Mean (SD)
Gender		
F	68.9 (10.7)	9.5 (7.1)
M	68.2 (10.4)	9.5 (7.0)
N excluded in analysis due to missing data	12	95
P-value from Student's T test	0.45	0.99
Race		
Black or African	70.4 (10.2)	5.7* (4.4)
Caucasian	68.7 (10.7)	9.7* (7.1)
Hispanic	65.4 (6.5)	7.3* (4.5)
Other	63.6 (11.5)	8.8* (6.6)
N excluded in analysis due to missing data	20	98
P-value from ANOVA	0.09	0.03
Insurance Classification		
Private	61.2* (9.2)	7.8* (5.8)
Public and Self-Pay	72.2* (9.1)	10.0* (7.3)
N excluded in analysis due to missing data	49	125
P-value from Student's T test	0.0001	0.005
Education		
< High School	71.1 (7.6)	6.9 (5.7)
Some High School, no degree	68.6 (16.1)	11.6 (7.7)
High School degree/GED	69.5 (10.4)	9.1 (7.7)
Some College, no degree	68.8 (11.5)	12.1 (8.9)
Associate degree	62.3 (7.0)	9.9 (7.3)
Bachelor's degree	66.8 (10.8)	8.9 (7.0)
Graduate or Professional degree	68.2 (10.2)	9.2 (6.0)
N excluded in analysis due to missing data	80	135
P-value from ANOVA	0.28	0.23
Years between Onset and Enrollment		
N excluded in analysis due to missing data	94	-
P-value from Regression Model	0.0001	-
Age		
N excluded in analysis due to missing data	-	94
P-value from Regression Model	-	0.0001

Table Seven – Multiple Regression Analysis

H&Y OFF Medication			
	Estimate	SD	P-value
Gender			
Female	0.11	0.07	0.10
Male	reference	-	-
Age	0.03*	0.01	0.0003
Years between Onset and Enrollment	0.07*	0.01	0.0001
Race			
Black or African	0.46*	0.22	0.03
Caucasian	reference	-	-
Hispanic	0.06	0.26	0.83
Other	-0.35	0.27	0.19
Insurance Classification			
Private	-0.03	0.08	0.71
Public and Self-Pay	reference	-	-

H&Y ON Medication			
	Estimate	SD	P-value
Gender			
Female	-0.001	0.08	0.99
Male	reference	-	-
Age	0.005	0.009	0.62
Years between Onset and Enrollment	0.03*	0.01	0.02
Race			
Black or African	0.26	0.25	0.31
Caucasian	reference	-	-
Hispanic	-0.02	0.30	0.95
Other	-0.14	0.32	0.65
Insurance Classification			
Private	-0.06	0.10	0.53
Public and Self-Pay	reference	-	-

Table Eight – Multiple Regression Analysis without Onset Data

H&Y OFF Medication			
	Estimate	SD	P-value
Gender			
Female	0.16*	0.07	0.01
Male	reference	-	-
Age	0.04*	0.01	0.0001
Race			
Black or African	0.05	0.21	0.83
Caucasian	reference	-	-
Hispanic	0.06	0.26	0.81
Other	-0.19	0.25	0.46
Insurance Classification			
Private	-0.04	0.26	0.62
Public and Self-Pay	reference	-	-
H&Y ON Medication			
	Estimate	SD	P-value
Gender			
Female	0.01	0.07	0.94
Male	reference	-	-
Age	-0.001	0.01	0.9
Race			
Black or African	0.33	0.23	0.16
Caucasian	reference	-	-
Hispanic	-0.11	0.28	0.69
Other	-0.21	0.08	0.14
Insurance Classification			
Private	-0.13	0.08	0.14
Public and Self-Pay	reference	-	-

Table Nine – Chi-Square Analysis of Complications

	Female (N=184)	Male (N=261)	P-value from Chi-square
Compulsive Behavior	10 (5.4%)	20 (7.7%)	0.35
Hallucinations	48 (26.1%)	74 (28.4%)	0.60
Dyskinesia	102 (55.4%)*	82 (31.4%)*	0.0001
Motor Fluctuations	111 (60.3%)*	115 (44.1%)*	0.0007
Dementia	33 (17.9%)	61 (23.4%)	0.16
Orthostatic Hypotension	24 (13.0%)	32 (12.3%)	0.81
Depression	44 (23.9%)	51 (19.5%)	0.27
Other Autonomic Dysfunction	23 (12.5%)	45 (17.2%)	0.17
Freezing	24 (13.0%)*	61 (23.4%)*	0.006
Psychosis	7 (3.8%)	7 (2.7%)	0.51

	Black or African (N=28)	Caucasian (N=375)	Hispanic (N=17)	Other (N=19)	P-value from Chi-square
Compulsive Behavior	2 (7.1%)	25 (6.7%)	0 (0.0%)	1 (5.3%)	0.50
Hallucinations	6 (21.4%)	106 (28.3%)	3 (17.6%)	5 (26.3%)	0.67
Dyskinesia	8 (28.6%)	152 (40.5%)	11 (64.7%)	8 (42.1%)	0.12
Motor Fluctuations	12 (42.9%)	186 (49.6%)	11 (64.7%)	11 (57.9%)	0.46
Dementia	4 (14.3%)	80 (21.3%)	4 (23.5%)	4 (21.1%)	0.82
Orthostatic Hypotension	5 (17.9%)	45 (12.0%)	1 (5.9%)	3 (15.8%)	0.63
Depression	3 (10.7%)	81 (21.6%)	5 (29.4%)	3 (15.8%)	0.37
Other Autonomic Dysfunction	3 (10.7%)	59 (15.7%)	2 (11.8%)	4 (21.1%)	0.76
Freezing	4 (14.3%)	69 (18.4%)	2 (11.8%)	7 (36.8%)	0.22
Psychosis	1 (3.6%)	13 (3.5%)	0 (0.0%)	0 (0.0%)	0.49

	Private (N=144)	Public and Self-Pay (N=262)	P-value from Chi-square
Compulsive Behavior	12 (8.3%)	18 (6.9%)	0.59
Hallucinations	25 (17.4%)*	84 (32.1%)*	0.001
Dyskinesia	51 (35.4%)*	120 (45.9%)*	0.04
Motor Fluctuations	66 (45.8%)	142 (54.2%)	0.11
Dementia	19 (13.2%)*	71 (27.1%)*	0.001
Orthostatic Hypotension	12 (8.3%)	36 (13.7%)	0.10
Depression	26 (18.1%)	64 (24.4%)	0.13
Other Autonomic Dysfunction	15 (10.4%)*	52 (19.8%)*	0.02
Freezing	24 (16.7%)	54 (20.6%)	0.33
Psychosis	2 (1.4%)	12 (4.6%)	0.07

Table Ten – Secondary Logistic Analysis

		Hallucinations			Dyskinesia	
	Odds ratio	Confidence Limits	p-value	Odds ratio	Confidence Limits	p-value
Gender						
Female:Male	0.84	0.74-1.93	0.46	2.35*	1.54-3.60	0.0001
Age	1.05*	1.02-1.08	0.0004	0.99	0.96-1.01	0.27
Race						
Caucasian:Black or African	1.48	0.59-4.26	0.41	1.96	0.84-5.01	0.12
Caucasian:Hispanic	1.42	0.43-6.44	0.59	0.45	0.13-1.32	0.15
Caucasian:Other	0.72	0.24-2.44	0.58	0.79	0.28-2.23	0.64
Black or African:Hispanic	0.96	0.20-5.36	0.96	0.23*	0.05-0.88	0.03
Black or African:Other	0.49	0.11-2.13	0.33	0.17	0.11-1.48	0.17
Hispanic:Other	0.51	0.08-2.71	0.43	1.75	0.41-8.11	0.46
Insurance Classification						
Public and Self-Pay:Private	1.38	0.77-2.53	0.28	1.75*	1.04-2.98	0.03

		Motor Fluctuations			Dementia	
	Odds ratio	Confidence Limits	p-value	Odds ratio	Confidence Limits	p-value
Gender						
Female:Male	1.76*	1.16-2.69	0.007	0.55*	0.32-0.93	0.03
Age	0.98*	0.95-0.99	0.05	1.06*	1.03-1.09	0.0002
Race						
Caucasian:Black or African	1.30	0.58-2.99	0.53	1.71	0.60-6.20	0.33
Caucasian:Hispanic	0.63	0.19-1.84	0.41	0.61	0.19-2.34	0.44
Caucasian:Other	0.52	0.17-1.44	0.21	0.66	0.20-2.58	0.52
Black or African:Hispanic	0.49	0.12-1.80	0.28	0.36	0.07-1.88	0.22
Black or African:Other	0.40	0.10-1.41	0.16	0.39	0.07-2.04	0.26
Hispanic:Other	0.82	0.18-3.77	0.79	1.08	0.19-6.11	0.93
Insurance Classification						
Public and Self-Pay:Private	1.85*	1.12-3.11	0.02	1.61	0.83-3.21	0.16

		Other Autonomic Dysfunction			Freezing	
	Odds ratio	Confidence Limits	p-value	Odds ratio	Confidence Limits	p-value
Gender						
Female:Male	0.55*	0.30-0.98	0.04	0.49*	0.27-0.85	0.01
Age	1.03*	1.00-1.06	0.05	1.04*	1.01-1.07	0.02
Race						
Caucasian:Black or African	1.55	0.50-6.80	0.48	1.27	0.45-4.54	0.67
Caucasian:Hispanic	1.19	0.30-7.87	0.83	1.10	0.28-7.27	0.91
Caucasian:Other	0.48	0.15-1.84	0.26	0.25*	0.09-0.76	0.02
Black or African:Hispanic	0.77	0.11-6.59	0.79	0.87	0.14-7.12	0.88
Black or African:Other	0.31	0.05-1.70	0.17	0.20*	0.04-0.86	0.03
Hispanic:Other	0.41	0.05-2.63	0.35	0.23	0.03-1.28	0.10
Insurance Classification						
Public and Self-Pay:Private	1.8	0.88-3.86	0.11	0.91	0.47-1.77	0.78

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CURRICULUM VITAE

William T. Cavanaugh

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Year of Birth: 1986

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EDUCATION:

M.S. in Medical Sciences

M.S. in Clinical Investigation 2013 - present

Boston University, Boston, MA

Relevant Courses: Biochemistry, Human Physiology, Management of Clinical Trials, Seminar in Clinical Research, Regulatory and Compliance Issues, Legal and Ethical Issues in Clinical Research, Behavioral Pharmacology

"Psychology in the Brain", taken at Harvard Extension School 2012

B.A. in Biology 2008

College of the Holy Cross, Worcester, MA

Relevant Courses: Cell Biology, Organic Chemistry, Physiological Psychology, Genetics, Biological Statistics, Cognitive Neuroscience, Undergraduate Study

EXPERIENCE:

Research Technician I 2008 - 2010

Research Technician II 2010 – 2013

Brigham and Women's Hospital/Harvard Medical School, Center for Neurologic Diseases

PIs: Dr. Dennis Selkoe, Dr. Matt LaVoie, Dr. Tracy Young-Pearse
Worked in an atmosphere of Molecular Mechanisms of Neurologic and Psychiatric Diseases

- Independent Project, APP (amyloid precursor protein) function using an APP conditional knockout mouse line
    - Intraperitoneal and subcutaneous injection of mice and rats
    - Troubleshooting injections at different developmental stages
    - Organ dissection
    - Vibratome and microtome sectioning
    - Immunostaining of multiple neural markers
    - Protein extraction, protein assays, and Western blotting
    - Supervised undergraduate student
    - Presented in lab meetings, participated in journal club

- Responsible for all animal colonies under Drs. Selkoe, LaVoie, and Young-Pearse
    - Tagged each mouse for identification
    - Maintained a working inventory of six different colonies, including matings (and checking for vaginal plugs), births, and deaths
    - Snipped mice tails to test DNA for genes specific to each colony
    - PCR and qPCR, and troubleshooting
- Assiting Dr. Young-Pearse with in utero surgeries on rats
    - Prepped animals for surgery
    - Sutured animals after surgery
- Laboratory Safety Officer

Undergraduate Research 2007-2008

College of the Holy Cross

Professor Mary Lee Ledbetter

- Cell culture
- Immunofluorescence of cells to see presence of connexin 43
- Dye transfer of cells to quantify cell-to-cell communication
- Radioactivity analysis to detect usage of sodium-potassium pump

ARTICLES:

Rice H, Suth S, **Cavanaugh W**, Bai J, Young-Pearse TL. In utero electroporation followed by primary neuronal culture for studying gene function in subset of cortical neurons. J Vis Exp. 2010 Oct 8;(44). pii: 2103. doi: 10.3791/2103. PMID:20972409

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ABSTRACTS:

S. Hong, O. Quintero-Monzon, J.R. Cirrito, B.L. Ostaszewski, T. Yang, **W.T. Cavanaugh**, D.M. Holtzman, D.J. Selkoe Aβ Economy *in vivo*: Microdialysis Reveals that Diffusible Aβ in Interstitial Fluid Falls as Plaques Accumulate with Age (Oral, *10th International Conference on Alzheimer's and Parkinson's Diseases*, Barcelona, Spain (2011)) Abstract #1184

Hong, S., Cirrito, J.R., Yang, T., Quintero-Monzon, O., **Cavanaugh, W.T.**, Holtzman, D.M. and Selkoe, D.J. Age-dependent Decrease of Interstitial Fluid Amyloid-β in APP Transgenic mice. Poster, *Society for Neuroscience 39th Annual Meeting*, Chicago, IL (2009).